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A.M.A. Archives OF SURGERY

Gastrocardiopexy

An Experimental Study

LESTER R. DRAGSTEDT II, M.D.
HERZL RAGINS, M.D.
EDWARD S. LYON, M.D.
and
LESTER R. DRAGSTEDT, M.D., Ph.D., Chicago

In 1951, Dragstedt, Oberhelman, and Smith [1] reported that transplantation of the antrum of the stomach into the transverse colon as a diverticulum in dogs produced a sustained hypersecretion of gastric juice with typical peptic ulcer formation. This observation prompted a study of the factors involved in producing this hyperactivity of the endocrine function of the antrum. It was soon found that tension within the antrum, especially that provoked by the hyperperistalsis associated with pyloric stenosis, was an even more profound stimulus to the endocrine function of the antrum than was contact with food or the primary products of digestion.[2] In subsequent experiments Heidenhain pouches were prepared in dogs for the quantitative collection of gastric secretion by methods previously described from this laboratory,[3] and later the antrum was transplanted as a diverticulum into the urinary bladder. It was hoped that the motility of the bladder associated with micturition would serve as a stimulus to antrum function and hypersecretion of gastric juice result. No stimulating effect, however, occurred, and, if any change was seen, it was in the direction of depression of gastric secretion. It seemed possible that the acidity of the urine in contact with the antrum mucosa might have inhibited gastrin release, since this phenomenon had previously been observed by us when acidified food was placed in contact with the mucosa of isolated antrum pouches. Accordingly, the present experiment was devised in which the lower half of the stomach was used as a pouch to envelop the heart in such a way that the beating of that organ would mechanically distend the antrum in a rhythmical fashion.

The present paper is a preliminary report of our observations to date. Dogs were operated upon under thiopental (Pentothal) ether, positive-pressure anesthesia, and the chest and abdomen were widely opened by a midline incision (Fig. 1). The stomach was transected at about its midportion and gastrointestinal continuity reestablished by gastrojejunostomy. The mucous membrane of the lower half of the stomach was then coned out, as in the Bancroft procedure (Fig. 2). Bleeding was controlled by a gastroenterostomy clamp placed across the upper duodenum and the dissection of the mucosa carried downward to the pylorus. In some experiments the dissection was stopped 3 or 4 cm. proximal to the pylorus, but in each case the lower mucosal cuff was ligated and inverted with a purse-string suture. By these means a seromuscular

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From the Department of Surgery of the University of Chicago. This work has been aided by grants from the Otho S. A. Sprague Memorial Institute and the Douglas Smith Foundation for Medical Research of the University of Chicago.

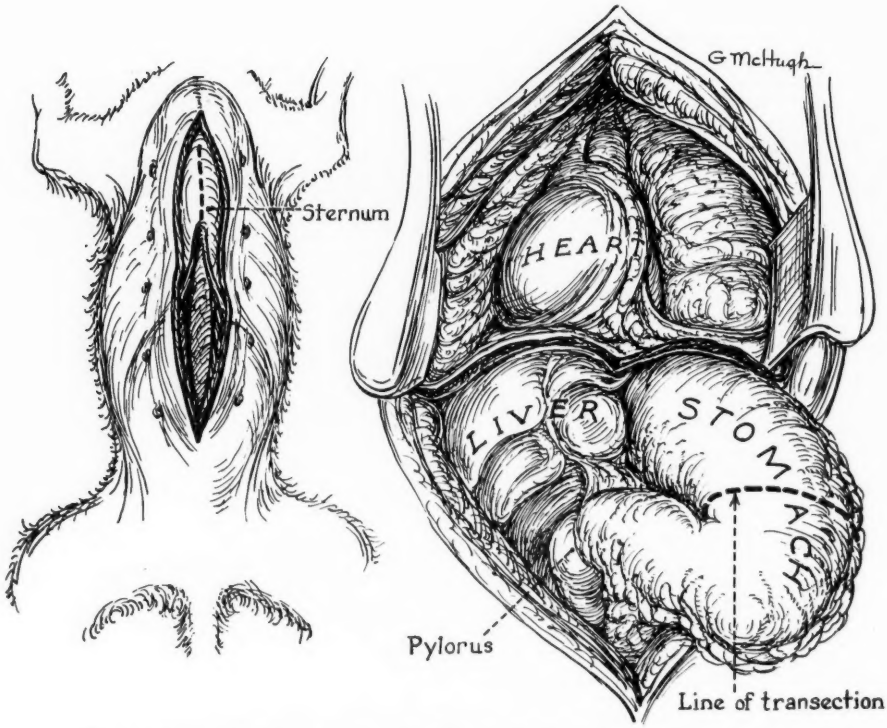

Fig. 1.—Drawings illustrating conversion of mediastinum and abdomen into a common cavity by a long midline incision extending through the diaphragm.

pouch of the lower half of the stomach in continuity with the duodenum and with an abundant blood supply was constructed. The pericardium was then widely opened and reflected and the epicardium roughened with the knife blade. After bleeding was controlled, the seromuscular pouch of the lower half of the stomach was placed around the heart and anchored to the auricles by interrupted silk sutures. When the operation was completed, all visible parts of the heart were enclosed by the stomach pouch (Fig. 3). The diaphragm was closed loosely around the pylorus, and the thoracoabdominal incision was closed without drainage.

Many animals succumbed to shock and hemorrhage, but seven survived the immediate postoperative period. Three of these dogs died within a period of two weeks, and at autopsy the antrum was found to be only loosely adherent to the heart, probably because of injection. Four animals survived in good condition and with no evidence of cardiac embarrassment. One of these dogs died after three months, and autopsy disclosed a large perforated gastrojejunal ulcer (Fig. 4). In this animal 4 cm. of antrum mucosa had been left proximal to the pylorus. The upper seromuscular pouch was firmly adherent to the epicardium on all sides (Fig. 5).

In our experience gastrojejunal ulcers rarely or never occur in normal dogs after either gastroenterostomy or partial gastric resection. The large gastrojejunal ulcer encountered in this experiment is suggestive evidence that a hypersecretion of gastric juice had been induced by the rhythmical distention of the antrum as a result of the gastrocardiopexy. Additional experiments will, of course, be required to verify this impression. The firm adhesion of the sero-

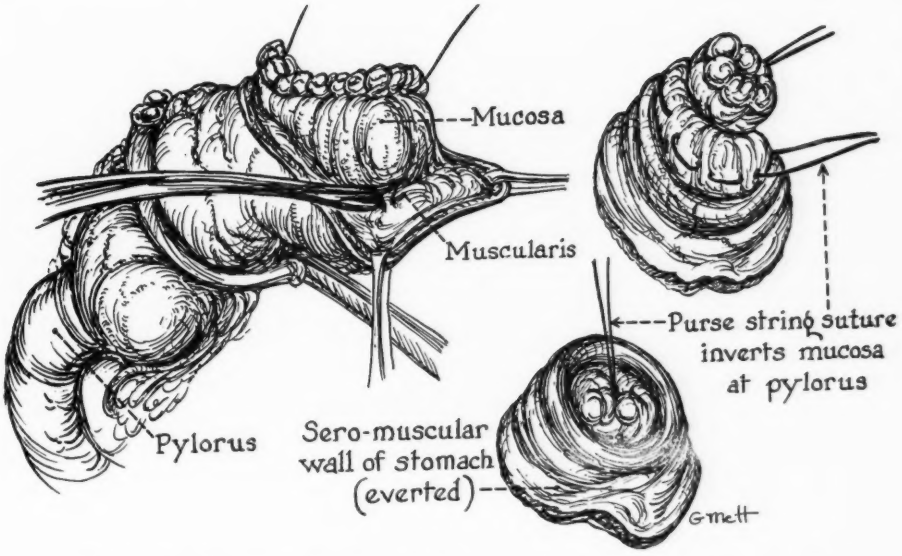

Fig. 2.—Drawings illustrating the method for excision of the mucosa of the lower half of the stomach, closure at the pylorus, and preservation of the blood supply to the seromuscular pouch of the antrum.

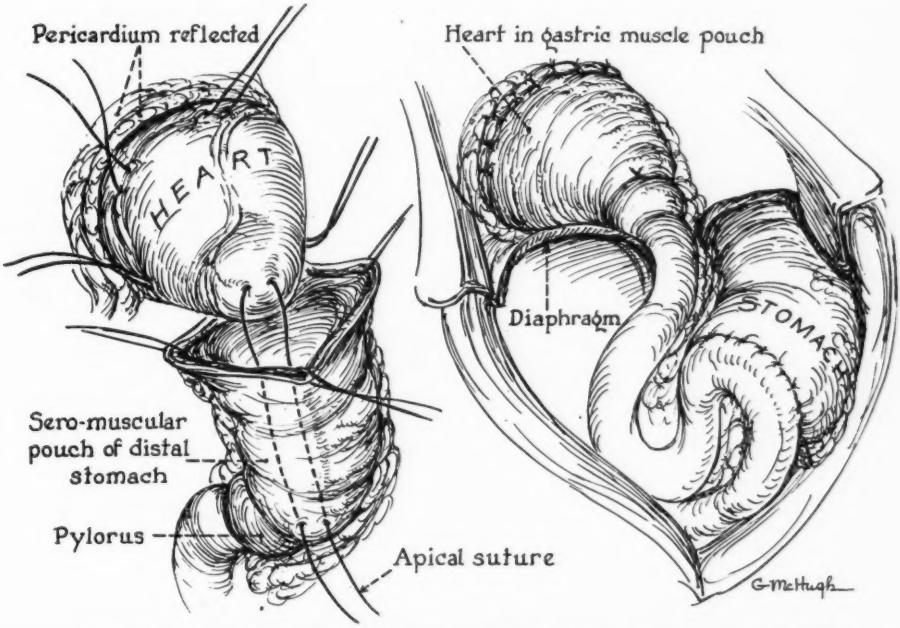

Fig. 3.—Drawings illustrating complete enclosure of the heart in the seromuscular pouch from the lower half of the stomach. Before enclosure in the pouch, the epicardium was roughened with a scalpel and dry gauze.

Fig. 4.—Photograph illustrating a large gastrojejunal ulcer, probably due to a hypersecretion of gastric juice of humoral origin induced by rhythmical distention of the antrum by the beating heart.

Fig. 5.—Photograph showing the firm adhesion between the seromuscular pouch of the lower half of the stomach and the heart.

muscular pouch of the stomach to the heart and its abundant blood supply form one of the reasons for this preliminary report. In contrast to some of the other methods devised for revascularization of the heart, in this procedure an additional covering of smooth muscle over the heart is provided which might conceivably be of value under certain conditions. Up to the present, however, we have not been able to secure evidence of direct vascular connections between the stomach pouch and the heart by the methods recommended by Beck and Leighninger.[4] As these investigators have justly pointed out, a procedure of this type can be used to determine the possible usefulness of a revascularization method.

Summary and Conclusions

Seromuscular pouches of the lower half of the stomach in dogs have been prepared by removal of the mucous membrane down to the pylorus. These pouches in continuity with the duodenum have been brought up through the diaphragm and sutured about the heart. Firm union between the gastric pouch and the heart occurs if the epicardium has first been abraded. Serious cardiac embarrassment does not occur. In one animal where the antrum had been left proximal to the pylorus, a perforating gastrojejunal ulcer developed, which may have been due to stimulation of the antrum by the rhythmical beatings of the heart.

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Intussusception in Adults

DAVID L. DEAN, M.D.
F. HENRY ELLIS JR., M.D.
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An intussusception is the invagination of a segment of the intestine into a contiguous portion of intestine. It usually takes place in a peristaltic direction, that is, the proximal segment invaginates into the distal segment. In occasional cases, the reverse is true—the so-called retrograde type of intussusception. Most intussusceptions occur in children less than two years of age and, as such, occur in the form of an acute surgical condition. Rarely does an intussusception occur in an adult. When it does occur in an adult, the symptoms are usually less severe and less dramatic in onset.

Ninety-six cases of intussusception occurring in adults have been encountered at the Mayo Clinic during the period from January, 1910, to January, 1955. It is the purpose of this paper to draw attention again to the occurrence of this disease in adults and to detail some of its characteristic features.

Incidence

It has been estimated that about 5% of all cases of intestinal obstruction are caused by intussusception [9] and that of all cases of intussusception, only 5% occur in adults.* Nevertheless, many cases of intussusception in adults have been reported in the literature. In 1911, Eliot and Corscaden reported on 300 such cases that they collected from the literature. Donhauser and Kelly collected 665 cases from the literature over the years 1900 to 1947. Deterling and associates reported 40 cases encountered at Presbyterian Hospital in New York over a period of 40 years. In a review of the records of the Mayo Clinic from 1910 to January, 1955, we found 96 cases of intussusception occurring among patients 15 years of age or older. Only those cases in which the diagnosis of intussusception was confirmed at operation have been included.

TABLE 1.—*Site of Intussusceptions in Adults (Ninety-Six Cases)*

Locations of Intussusceptions			Cases	
			Number	Per Cent
Enteric	Duodenojejunal	1	29	30.21
	Jejunojejunal	10		
	Jejunojejunojejunal	1		
	Ileoileal	16		
	Exact site not described	1		
Ileocecal		29	29	30.21
Ileocolic	Simple	4	6	6.25
	Ileoileocolic	2		
Colocolic	Ascending colon	3	32	33.33
	Transverse colon	10		
	Descending colon	3		
	Sigmoid colon	15		
	Rectum	1		
Total			96	100.00

Etiologic Factors

Intussusception in adults in contrast to the disease occurring in infants is usually the result of a demonstrable organic lesion. An increase in peristaltic activity caused by an intraluminal tumor of some sort is usually the initiating factor. This lesion is carried down the intestine by peristalsis and pulls with it a segment of intestine, the tumor, in most cases, forming the apex of the invaginating segment. Retrograde intussusception following removal of a Miller-Abbott tube has been reported.

Recorded for publication Oct. 19, 1955.

Fellow in Surgery, Mayo Foundation (Dr. Dean). Section of Surgery (Dr. Ellis); Section of Medicine (Dr. Sauer), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

* References 1, 6, and 7.

Intussusception is best classified as to location. The four common types are (1) enteric, in which one segment of small bowel invaginates into another segment of small bowel; (2) ileocecal, in which the ileocecal valve becomes the leading point of the intussusception; (3) ileocolic, in which the ileum goes through the ileocecal valve, the cecum staying in situ, and (4) colocolic, in which one segment of colon invaginates into another segment of colon.

which were encountered at operation and which were considered to be responsible for the development of the intussusception in these 96 cases. In 87.5% of cases an organic lesion responsible for the disease was found. Of the 84 lesions 58 or 69% were malignant.

Signs and Symptoms

Only 13 cases (13.5%) presented the picture of acute intestinal obstruction. The symptoms more commonly were of several

TABLE 2.—*Causes of the Intussusceptions*

	Large Intestine	No.	Small Intestine	No.	Total Cases	
					Number	Per Cent
Malignant neoplasms	Carcinoma, cecum	19	Carcinoma, jejunum	2		
	Carcinoma, sigmoid	12	Carcinoma, ileum	2		
	Carcinoma, other parts of colon	14	Reticulum-cell sarcoma, ileum	2		
	Lymphosarcoma of descending colon	1	Sarcoma, ileum	1		
	Lymphosarcoma, cecum	1	Myosarcoma, ileum	1		
			Fibrosarcoma, ileum	1		
			Lymphosarcoma, ileum	1		
			Squamous-cell carcinoma, ileum	1		
	Total	47	Total	11	58	60.4
Benign neoplasms	Lipoma	6	Lipoma	4		
	Leiomyoma	1	Polyp	2		
	Multiple polyps	1	Heterotopic gastric mucosa	1		
			Myxoma	1		
			Fibromyxoma	1		
	Total	8	Total	9	17	17.7
Idiopathic type	Ileocecal	4		8	12	12.5
Meckel's diverticulum					4	4.2
Miscellaneous		3		2	5	5.2
Total					96	100.0

The ileocecal type is the commonest type of intussusception seen among infants and accounts for 65% to 90% of cases reported in different series.† In adults the location of the intussusception is more evenly divided among the different parts of the bowel. Table 1 shows the location of the intussusceptions in this group of 96 cases. In three cases the intussusceptions were compound —two ileoileocolic and another jejunojejunojejunal. Table 2 is a list of the lesions

† References 1, 5, and 9.

months' duration and often were not very severe or incapacitating; 63.3% of the patients had had significant symptoms for one month to one year. The commonest symptom, which occurred in 73% of the cases, was the presence of intermittent abdominal cramping pain. This was sometimes associated with a change in bowel habits. A mass was palpated on examination of the abdomen in 42% of the cases, and in several other cases a mass was felt on rectal examination. The passage of gross blood per

rectum occurred in 29% of the cases. In a few cases the low-grade intestinal obstruction that was chronic and partial became acute and complete. Table 3 shows the incidence of the commoner symptoms, many of which often were present in the same patient.

TABLE 3.—*Incidence of Common Symptoms of Intussusception*

Symptoms	Incidence
Cramps	71
Constipation	21
Diarrhea	25
Melena	28
Loss of weight	13
Vomiting	13

Roentgenographic examination often is diagnostic in intussusception. A barium enema is usually the best method of demonstrating such a lesion, though at times a simple roentgenogram of the abdomen may show it. Schatzki reported that an ordinary roentgenogram of the abdomen in some cases will show a sausage-shaped homogeneous shadow outlined by two stripes of air or by concentric rings of lighter density representing the air-filled sheath. In the barium-enema examination the barium may appear to stop suddenly with the formation of a "cap" corresponding to the head of the intussusception. More typically, the barium enters the space inside of the intussusceptiens but outside of the intussusceptum. This gives a picture of two parallel lines of barium connected by concentric rings of barium and has been described as a "spiral sheath" or as giving a "coiled spring appearance" (Fig. 1). In 28 cases, 29.1% of the cases in this report, the roentgenographic examination was diagnostic of intussusception.

Fig. 1 (Case 1).—Barium enema showing "coiled spring" appearance.

Treatment

In general there are two methods of treatment for intussusception—surgical or nonsurgical. The latter entails reduction of the intussusception by hydrostatic pressure by means of an enema. This method has been recommended for the treatment of intussusception in infants. Many physicians have claimed good results with it, whereas others have shown that it may be dangerous. Whether or not one agrees with the therapeutic use of the barium enema for intussusception in infants, the high incidence of organic lesions as the cause of the intussusception in adults excludes this method as a definitive therapeutic measure for patients in this age group. Brayton and Norris, however, have suggested reducing the intussusception by barium enema under fluoroscopy, thereby relieving the obstruction and gaining time to prepare the bowel for definitive surgery at a later date.

At the time of operation the intussusception is reduced, if possible. If the cause of the intussusception is not readily apparent, a thorough search for an organic lesion is made. In infants and young children usually none will be found, but in adults the opposite is true. The causative lesion must be removed, and in many cases segmental resection and end-to-end anastomosis is the procedure of choice. A more radical resection may be required to remove certain ma-

lignant lesions or extensive gangrenous regions. A transcolonic or transenteric removal of some obviously benign lesions may be possible. Table 4 shows the various operative procedures employed in these 96 cases.

TABLE 4.—*Operative Procedures Employed for Intussusception in Adults*

Operations Performed	Number of Cases
Resection and end-to-end anastomosis	53
Exteriorization resection	16
Resection and end-to-side or side-to-side anastomosis	8
Reduction and transenteric removal of lesion	3
Reduction and excision (Meckel's diverticulum)	3
Reduction only	6
Reduction and ileopexy	1
Reduction and closure of perforation	1
Two-stage abdominoperineal resection	1
Colostomy, then posterior resection	1
Cecostomy and strangulation resection by rubber band over tube in intussusception	1
Temporary colostomy	1
Colectomy (for chronic ulcerative colitis)	1
Total	96

The following two reports of cases will serve to illustrate some of the variable features of this disease in adults.

Report of Cases

CASE 1.—A 23-year-old white man came to the Mayo Clinic because of "stomach trouble" of 9 months' duration. He had been having intermittent cramping pains in the upper portion of the abdomen slightly to the right of the midline for the past nine months. These pains were not related to intake of food and he had not had nausea, vomiting, or jaundice. He had noted some belching. His bowel movements were more frequent, occurring two to three times a day instead of the usual once. Two months prior to admission, and again two weeks previously, he had had episodes of rectal passage of bright-red blood. His symptoms were not severe or incapacitating. However, he was hospitalized because his pain became severer, he vomited several times, and rectal bleeding recurred.

Physical examination revealed a well-nourished white man with acute abdominal pain. General examination was noncontributory, except for the abdominal findings. The abdomen was soft with only minimal tenderness in the right lower quadrant. The first examiner's note stated, "There appear to be thickened dilated loops of bowel in the right lower quadrant and palpitation precipitates a bout of severe cramping pain." Normal peristaltic sounds were present. Rectal examination showed red blood on the stool. A plain roentgenogram of the abdomen did not show evidence of any abnormality. Results of tests of blood and urine were within normal limits.

It was believed that the picture was not that of an acute surgical abdomen, and 24 hours after treatment with nasogastric suction and intravenous fluids he had improved. He tolerated oral intake of fluids for one day but then vomited again, and his abdomen became moderately distended. At this time a poorly defined, soft mass became palpable in the right lower quadrant. A barium enema was given without any cathartic preparation and an intussusception was demonstrated (Fig. 1). The radiologist described an intussusception of the right portion of the colon in which the cecum had progressed to the midtransverse colon.

Operation was carried out, and a compound intussusception was found. The ileum, together with a Meckel's diverticulum, had intussuscepted into the distal portion of the ileum, and this portion of the bowel had in turn intussuscepted into the colon, forming a compound intussusception, the apex of

Fig. 2 (Case 1).—Gross specimen after the intussusception was partially reduced, showing the colon at the left and the ileum with Meckel's diverticulum at the right.

which reached to the midtransverse colon (Fig. 2). Neither intussusception could be reduced; therefore, right hemicolectomy and end-to-end anastomosis between the ileum and the transverse colon were carried out.

The patient had an uneventful postoperative recovery.

Comment.—This case is an example of a benign lesion causing recurrent episodes of abdominal pain leading eventually to an acute episode necessitating surgical exploration and resection of a strangulated intussusception.

CASE 2.—A 68-year-old white man had a 5-week history of constant pain in the lower part of the abdomen. Prior to this he had been well. For five weeks he also had had alternating diarrhea and constipation. He had passed bright-red blood rectally on two occasions, two weeks and one week prior to his admission. Superimposed on the constant pain, which was not severe, he had a "feeling of a knot tightening up, then loosening" in his abdomen.

His past history was noncontributory. He had been seen at the Mayo Clinic four years earlier, at which time a diagnosis of degenerative cerebellar lesion was made. He still complained of the incoordination of gait found at this prior examination.

On physical examination a soft mass the size of a grapefruit was palpated in the right lower quadrant. Rectal examination gave negative results. The only other positive finding was the absence of tendon reflexes in the lower extremities.

A roentgenogram of the colon showed evidence of an "intussuscepting carcinoma of the cecum. It was first encountered in the transverse colon and was then reduced by the barium enema" (Fig. 3). Tests of blood and urine showed results within normal limits.

Operation was performed and an intussuscepting carcinoma of the cecum was found which, at the time of exploration, had reached the midtransverse colon. This was reduced readily. Neither enlarged nodes nor metastasis to the liver was apparent. Right hemicolectomy with a side-to-side ileotransverse colostomy was done. Postoperatively the patient did well and was well when last heard from seven years later.

Comment.—This case presents an example of a malignant lesion giving rise to intussusception with a chronic course. The diagnosis of an intussusception was made by means of a barium enema.

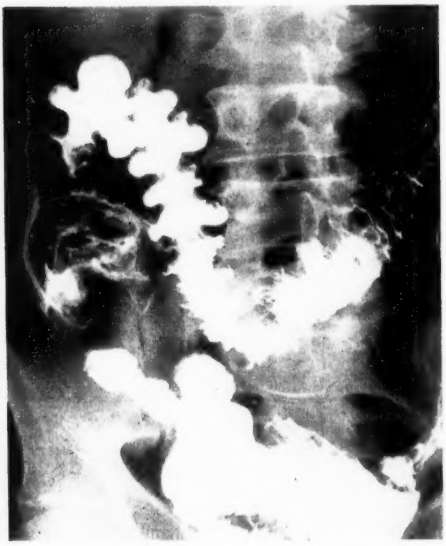

Fig. 3 (Case 2).—Barium enema showing an intussuscepting cecal lesion which has been reduced to the right portion of the colon from the transverse colon where it was encountered.

Summary

A brief review is presented of 96 cases of intussusception in adults encountered at the Mayo Clinic from 1910 to 1955. In 87.5% of the cases an organic lesion was the cause of the intussusception; in 69% of these cases the organic lesions were malignant. Various methods of treatment are discussed. It is emphasized that the high incidence of organic lesions makes surgical treatment mandatory for intussusception in adults. Reports of two typical cases are included.

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Choledochojejunostomy en Roux Y

An Experimental Study

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Chronic relapsing pancreatitis has proved a challenge to both the internist and the surgeon, and because of an inability to control the natural course of the disease by conservative medical therapy it has become a surgical problem. A common etiological factor for all cases of pancreatitis has not been generally accepted. The relief of symptoms by biliary diversion operations, such as choledochojejunostomy en Roux Y as described by Bowers and Greenfield,* and elimination of sphincter of Oddi obstruction by sphincterotomy, as described by Mulholland and Doubilet,† suggests that a common pathway for drainage of both biliary and pancreatic secretions with obstruction at the sphincter of Oddi and resultant biliary regurgitation into the pancreas is a frequently encountered cause of chronic relapsing pancreatitis.

Choledochojejunostomy en Roux Y [7] is accomplished by a primary division of the jejunum 10 to 12 in. below Treitz's ligament, with a distal implantation of the proximal end 12 to 18 in. below the site of the primary jejunal division to form the defunctionalized Roux-Y loop. The common duct is divided and implanted into the end of the defunctionalized segment. This results in a total biliary by-pass to the jejunum 22 to 30 in. below Treitz's ligament. Significant regurgitation of bile into the duodenum proximal to the site of enteroenterostomy is unlikely. In view of the many reports ‡ relative to the incidence of duodenal ulceration following the formation of biliary fistulae of both the external and internal types, it was felt desirable to evaluate choledochojejunostomy en Roux Y experimentally as to its ulcer-forming potentials.

Literature

Various procedures have been used to produce internal biliary fistulae in dogs, with variable results. Kapsinow [21] anastomosed the fundus of the gall bladder to the right renal pelvis. After ligation of the common duct creating a total biliary exclusion, 17 of 43 dogs developed typical duodenal ulcerations. Weiss and Gurriaran § reported the presence of duodenal ulcer formation in one of three dogs following ligation of the common duct and anastomosis of the gall bladder to the terminal ileum. Owings and Smith ‖ ligated the common duct and performed a cholecystoenterostomy 18 in. distal to Treitz's ligament in five dogs and reported the formation of duodenal ulcers in two animals. Graves,[16] performing a similar internal bile exclusion procedure, reported pyloric ulcerations in one of eight surviving animals. After reviewing the reported results of internal biliary fistula formation, Ivy, Grossman and Bachrach [18] compiled an ulcer incidence of 39%.

While studying the protective value of alkaline duodenal secretions, DeBakey [10] performed a pyloric occlusion with gastrojejunostomy just distal to Treitz's ligament and transplanted the common duct into the terminal ileum. Ninety per cent of the ani-

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* References 4-7.

† References 11-13.

‡ References 1, 2, 3, 14, 15, 19, 20, 22, 23, 24, 28.

§ References 29 and 30.

‖ References 25 and 26.

mals developed jejunal ulcers during periods of observation varying from 7 to 60 days. This suggested that bile was the most important protective element of the alkaline duodenal secretions. Hebert [17] found that the gastric acidity and amount of gastric secretion in the fasting stomach was increased in the presence of biliary obstruction and that the buffering action of the duodenum and its contents was definitely reduced. Graves [16] reported that after selective biliary or pancreatic diversion into the lower intestine the remaining duodenal secretion prevented duodenal ulceration. The possible mechanisms of ulcer formation following biliary exclusion procedures have been reviewed by Ivy and co-workers [18] who considered the available data insufficient for any conclusion. Regardless of the process of ulcer formation following total biliary exclusion procedures, it is apparent from the reported experimental work that a significant number of ulcerations will occur after such procedures.

Material and Methods

Healthy mongrel dogs weighing 11 to 16 kg. (25 to 35 lb.) were used, and all operations were performed under intravenous pentobarbital sodium anesthesia with aseptic technique. A total of 88 animals were subjected to choledochojejunostomy en Roux Y utilizing the following technique: The jejunum was divided at the site of the first major vascular arcade, 2 to 5 in. distal to Treitz's ligament (Fig. 1, *A*). The distal end of the jejunum was closed. The proximal end of the jejunum was anastomosed end-to-side to the jejunum 15 in. distal to the site of the primary division. The common duct was divided close to the duodenum after proximal ligation of the duct and implanted along the antimesenteric margin of the defunctionalized loop through a small stab wound by the Coffey technique [9] (Fig. 1, *B*).

Thirty-eight of these animals were excluded from the final evaluation because of death due either to unrelated complications with an inadequate period of observation or to a significant degree of biliary obstruction at the site of choledochojejunostomy with cholangitis.

The remaining 50 dogs were divided into two groups of 25 animals each and treated as follows:

GROUP 1.—These animals were maintained on regular animal rations with canned meat and milk

Fig. 1.—*A*, choledochojejunostomy en Roux Y as used in this series. *B*, method of implantation of the common duct by the Coffey-3 technique.

supplements and observed for periods varying from 16 to 97 days postoperatively. Animals dying from other causes but without cholangitis and surviving operation for a minimal period of 16 days were included in the series. The earliest duodenal ulcer was observed 16 days after biliary diversion.

GROUP 2.—This group was maintained on regular animal rations with canned meat and milk supplements. Fourteen days postoperatively, histamine base in liquid petrolatum (mineral oil) and yellow wax (beeswax) 30 mg. daily [8] was given intramuscularly for a period of thirty days. Animals surviving the total histamine course were killed.

GROUP 3.—Twenty dogs constituted the control group and received histamine base in liquid petrolatum and yellow wax 30 mg. daily [8] for a period of 30 days prior to being killed.

All animals were autopsied at the time they died or were killed, and the gross specimens were preserved and sections taken for microscopic study.

Results

The common ducts of all animals showed evidence of dilatation distal to the site of choledochojejunostomy and were found to vary in size from 3 to 5 mm. in diameter. The findings of Sandblom and co-workers [27] that dilatation of the bile duct constantly followed an anastomosis of the biliary tract to the intestine in experimental animals was confirmed. Significant obstruction was assumed to be absent when clear bile could be expressed from the implanted common duct with light pressure on the gall bladder, when the defunctionalized loop was found to contain bile prior to the application of pressure, and when a probe could be passed through the anastomosis into the common duct without resistance. Routine bile cultures were not taken, but liver specimens were carefully examined for microscopic evidence of cholangitis.

GROUP 1. — *Choledochojejunostomy en Roux Y Without Histamine base.*—Twenty-three animals showed evidence of thickening of the mucosal layer of the duodenum and jejunum, which varied in degree from minimal to marked thickening with loss of the normal intestinal folds (Table 1). Nine were classified as mild in degree and fourteen as moderately severe or severe. In the severe cases the mucosa was covered with a thick tenacious bloody mucoid secretion. In five specimens mucosal changes were noted in the jejunum to a point approximately 10 cm. proximal to the site of enteroenterostomy. Bile was seen regurgitating into the distal normal segment.

Thirteen (52%) of the group were found to have duodenal ulcerations (Table 2). Four had solitary ulcers measuring 1 to 3

TABLE 1.—*Duodenitis and Jejunitis in the Three Groups*

Results	Group 1 Choledochojejunostomy en Roux Y, 25 Dogs		Group 2 Choledochojejunostomy en Roux Y, 25 Dogs (Histamine)		Group 3 Histamine Base Control, 20 Dogs	
	No.	%	No.	%	No.	%
Duodenitis & Jejunitis	23		21		18	
(*a*) Mild to moderate	9	39	8	38	8	44
(*b*) Moderately severe to severe	14	61	13	62	10	56

TABLE 2.—*Peptic Ulceration in the Three Groups*

Results	Group 1 Choledochojejunostomy en Roux Y, 25 Dogs		Group 2 Choledochojejunostomy en Roux Y, 25 Dogs (Histamine Base)		Group 3 Histamine Base Control, 20 Dogs	
	No.	%	No.	%	No.	%
Peptic ulceration	13		19		8	
(*a*) Ulcer-solitary	4	31	9	47	6	75
(*b*) Ulcer-multiple	9	69	10	53	2	25
(*c*) Perforations	1	8	5	26	0	0
(*d*) Impending perforation	2	16	3	16	0	0

cm. in diameter distal to the pylorus, and nine had multiple ulcers which were usually localized to the proximal duodenum. One animal died of peritonitis due to ulcer perforation on the 16th postoperative day, and two were classified as having impending ulcer perforation at the time they were killed.

GROUP 2. — *Choledochojejunostomy en Roux Y Histamine Base, Thirty Milligrams Daily for Thirty Days.*—Twenty-one dogs (84%) developed the characteristic duodenal and jejunal changes previously described, 62% of which were classified as moderately severe or severe (Table 1).

dogs received histamine base, 30 mg. daily, until they were found dead or were killed after 30 days of continuous treatment.

Eighteen dogs (90%) developed duodenitis and jejunitis described as moderately severe or severe in 56% (Table 1). Eight animals (40%) developed typical duodenal ulcers varying in size from 8 mm. to 3.5 cm. along the antimesenteric margin of the duodenum (Table 2). Solitary ulcers were found in six, multiple ulcers in two. In all cases these were confined to the proximal duodenum. No perforations or impending perforations were found in the series.

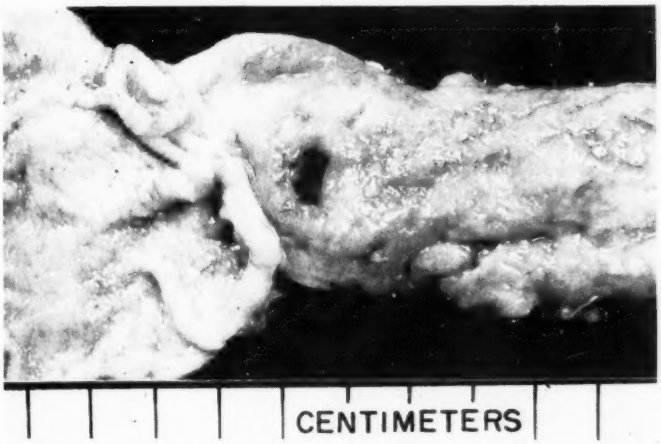

Fig. 2.—Specimen from region of pylorus, Dog 1937, showing typical duodenal ulcer and duodenal mucosal reaction 45 days after choledochojejunostomy.

Nineteen animals (64%) developed typical duodenal ulcerations (Table 2). Nine of these were single ulcers varying in size from 1 to 3 cm. in diameter, and 10 animals presented multiple ulcerations varying in size from 2 mm. to 1 cm. in diameter involving both duodenum and jejunum. These were true ulcers with precipitous walls showing varying degrees of penetration of the muscularis mucosa (Fig. 2). Five animals died of generalized peritonitis due to perforation of one or more duodenal ulcerations on days 2, 4, 4, 15, 26 following the onset of histamine therapy. Three animals were found to have impending ulcer perforations at the time of autopsy.

GROUP 3.—*Histamine Control.*—Twenty

Comment

It is apparent from these experimental animals that two major changes have occurred in the gastrointestinal tract after the internal diversion of bile by the choledochojejunostomy en Roux Y technique. In Group 1, 92% receiving no histamine developed some degree of duodenal and jejunal mucosal reaction, 61% of which reactions were classified as moderately severe to severe. This change is given a descriptive classification here as duodenitis and jejunitis based only upon the gross appearance of the bowel. Microscopically, these changes were found to be secondary to glandular hypertrophy with cellular mucoid distention rather than inflammatory reaction (Fig. 3). The

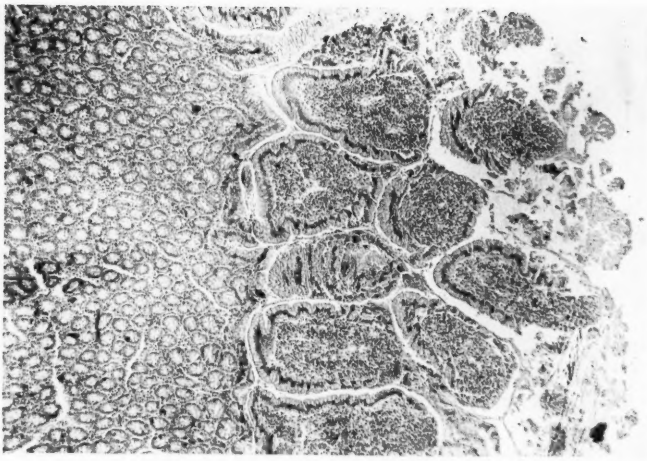

Fig. 3.—Photomicrograph of duodenal mucosa showing glandular hypertrophy and mucous-secreting cells; × 100.

presence of blood-stained secretion in the lumen of the bowel indicated that the intestinal bleeding may occur on this basis despite the absence of acute or chronic ulcerations. Similar changes were noted in 90% of the histamine control series, with 56% being recorded as moderately severe to severe. Histamine stimulation following choledochojejunostomy resulted in similar changes in 84% of the dogs, with 62% of these being classified as moderately severe or severe. Gross studies of the autopsy specimens revealed that the severity of the reaction decreased abruptly in the immediate vicinity of the enteroenterostomy, and in five specimens the transitional change could be definitely demonstrated 10 cm. proximal to this point. This was also the gross level of bile regurgitation. By inference, then, it appeared that the jejunal mucosal changes were altered by the regurgitated bile.

Duodenitis and jejunitis of mild to moderate severity was found in normal laboratory animals not subjected to operation. In no case was the degree of reaction in these animals as advanced as those described in this study as moderately severe or severe, and it was concluded that only the more advanced changes were of experimental significance. No evidence of intraluminal hemorrhage was found in the normal animals. The duodenal and jejunal mucosal changes of significant degree appeared with equal frequency in each series of animals (Table 1).

Duodenal ulcer formation occurred in 52% of the animals in the choledochojejunostomy series without histamine (Table 2). Thirty-one per cent of these were solitary ulcers, and sixty-nine per cent were multiple ulcerations. A single animal had perforation with resultant peritonitis, and two animals showed impending perforation at the time of autopsy. Comparison of these results with the histamine control group reveals that 40% of the normal animals receiving histamine base developed ulcers, of which six were single and two were multiple ulcerations. There were no perforations or impending perforations. Choledochojejunostomy en Roux Y alone and histamine stimulation of normal animals produced a comparable number of duodenal ulcers with a suggestion that the reaction is more severe in the biliary diversional group in view of the increased frequency of multiple ulcers and the presence of one ulcer perforation and two impending perforations.

When histamine base was given to animals following choledochojejunostomy, several factors became apparent. The number of duodenal and jejunal ulcerations increased

to 76% of the total group, as compared with an ulcer incidence of 52% in Group 1. Twenty-six per cent died of peritonitis due to ulcer perforation prior to the completion of the 30 days of histamine-base therapy, and sixteen per cent were found to have impending perforations at the time they were killed. A deliberate attempt to increase the gastric acidity following choledochojejunostomy had caused a higher incidence of peptic ulcers and increased the activity of the ulcers, as evidenced by the larger number of perforations or impending perforations.

The application of these experimental findings to clinical patients subjected to choledochojejunostomy is not intended, but certain clinical implications of the study are clearly defined. The use of a total internal biliary exclusion procedure, such as choledochojejunostomy en Roux Y, in the treatment of clinically benign conditions must still be considered to be within the experimental category. Final evaluation of the operation as to the creation of an ulcer diathesis can be made only when additional cases have been added to the reported operative series with longer follow-up periods. The frequent association of chronic alcoholism and chronic recurrent pancreatitis is well known. A comparison of the choledochojejunostomy series—Group 1, without histamine, and Group 2, with histamine—suggests that the combination of (1) the absence of bile neutralization, (2) the hyperacidity secondary to the ingestion of alcohol, and (3) the elimination of a normal dietary intake characteristic of the alcoholic minimizing the effects of protein-acid neutralization would establish the necessary conditions for ulcer formation. It is believed that careful dietary management should be mandatory in all patients subjected to the operation during their entire postoperative life.

Summary

In dogs choledochojejunostomy en Roux Y resulted in an incidence of 52% of peptic ulcer formation during periods of observation from 16 to 97 days, as compared with 40% following histamine stimulation in control animals. After choledochojejunostomy with histamine stimulation postoperatively, ulcer incidence was 76%, with an increase in the number of perforations and impending perforations. This work indicates that the internal diversion of bile by the choledochojejunostomy en Roux Y technique in dogs creates an ulcer diathesis. The clinical implications of the study are discussed.

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Editorial

REGARDING POSTCHOLEDOCHOJEJUNOSTOMY ULCERS IN THE HUMAN

ONE OF the two distinct disadvantages to the operation choledochojejunostomy en Roux Y is the possibility of formation of peptic ulcer which may arise when the duodenum is denied one of the neutralizers in the form of bile, which, of course, is shunted away from the duodenum into the distant defunctionalized jejunum. The other disadvantage involves transection of the common duct, a maneuver which no knowing surgeon wishes to negotiate. Experiences with the operation do not substantiate the fear of cutting the duct because postoperative incidents, such as stricture, cholangitis or nonulcer physiological disturbances, have not been great enough in number to be significant. Moreover, most students of the disease known as recurring or relapsing pancreatitis agree that the ravages of the disease are so terrifying that some risk and well-studied use of radical procedures are justified if the disease can be controlled by these measures. Successful control can be obtained, when the patients are carefully selected, in about 80% of the cases.

It is sometimes stated that the deranged physiology resembles the Mann-Williamson dog preparation. This is not the case for two reasons. The alkaline pancreatic secretion is unchanged in the duodenum of the surgically treated patient, and Brunner's glands, which produce abundant alkaline mucus in the

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duodenum of man, are relatively scarce in the dog's duodenum. The human duodenum should possess therefore a greater resistance to ulceration than the dog's duodenum. Kehne and Campbell, reporting in this issue of the A. M. A. ARCHIVES OF SURGERY, have tested the ulcer formation after choledochojejunostomy in the experimental animal and have noted 76% ulceration after histamine stimulation and approximately 52% ulceration without this stimulus. There can be no doubt therefore that the operation aids the formation of peptic ulcer in the normal laboratory dog.

Realizing the importance of animal experimentation, one naturally would postulate that the number of postcholedochojejunostomy ulcers in human beings may be great or frequent enough to cause alarm about its use. Fortunately, there is opportunity to recognize and list the number of such ulcers, if they should appear, as many surgeons perform this operation for trauma, for common-duct obstruction which cannot be relieved by simple means, for pancreatitis, and as palliation in malignancies of the pancreas. Some of the early surgeons have stated that these ulcers do not occur. A small number of other writers describe an occasional ulcer, and several surgeons mention that they appear after choledochojejunostomy, but no well-documented study of the problem is available as far as I know. If these ulcers are present in any great number, their presence is not reported.

Several things seem apparent. There would be no question that peptic ulcer would appear promptly in the patient who undergoes choledochojejunostomy if he has what is known as the "ulcer diathesis"—more properly perhaps if the patient demonstrates high gastric acidity in volume and degree.

It must be remembered that peptic ulceration is not a common sequel to carcinoma of the head of the pancreas, even though common-duct obstruction is due to the disease process or the bile has been surgically shunted for palliative relief. In these instances, the duodenum is denied this important neutralizer. Indeed it is denied also the neutralizing effect of pancreatic juice, which is not the case when choledochojejunostomy is performed for pancreatitis. One could well argue that in these malignancies hypochlorhydria is more frequently the case and this low-acid state protects the patient from ulceration.

The facts stated above then suggest that if the patient demonstrates normal or low gastric acidity peptic ulceration should not be often found after the operation. Of sixteen pancreatitic patients subjected to choledochojejunostomy en Roux Y, all demonstrated normal or low gastric acidity pre- and postoperatively. Twice the operator explored the abdomen with choledochojejunostomy in mind, but the exploration revealed the fact that the pancreatitis was secondary to duodenal ulcer with pancreatic penetration, and control of pancreatitis in these two instances was had by gastric resection plus vagotomy. If choledochojejunostomy had been performed in these two patients, the ulcer status would have been worsened. Consequently, proper selection before and at the time of the operation probably keeps the postcholedochojejunostomy ulcer at a low-incidence rate. Several choledochojejunostomies for inoperable carcinoma of the pancreas have been performed when the "infection-versus-tumor" differential could not be accurately established. One patient was suspected of ulcer formation which could not be verified by x-ray. The patient's death was undoubtedly due to carcinoma, but autopsy was not permitted. Kehne, working in our clinic, was quite convinced that ulcers would appear in these patients

and was invited to interview and examine these patients when they returned for follow-up studies. I suspect there was some element of disappointment when he could find none. Some of the patients are now seven and one-half years postoperative. Nevertheless, we chose to subject the operation to close scrutiny in the animal laboratory and observed the ulcer formation after the operation in dogs. Could the caged dog because of his strange confinement possibly undergo the same stress and strain of the modern ulcer patient? What protects the animals which do not develop ulcers? The operation is the same, and even of these ulcerophilic laboratory animals some do not develop the ulcers.

Clinically, we have not dared to employ choledochojejunostomy in the "burning-out" or "burnt-out" pancreas not only because control is doubted but also because with both neutralizers absent in the duodenum peptic ulcer should be commonly observed after the operation.

It appears, then, that no one has observed large numbers of peptic ulcers develop after choledochojejunostomy en Roux Y, although statements about the fear of ulcer formation in these patients are often made. A low postoperative rate will probably result in properly selected patients if a normal or low gastric acidity is demonstrated, if the pancreatitis is not due to primary duodenal ulcer, or if the disease does not represent an infected pancreas near the "burnt-out" state.

Most surgeons believe that medical or surgical therapy can control nearly all peptic ulcer cases. Pancreatitis is a dreaded and tragic disease. If an occasional gastric resection plus vagotomy should be necessary to correct the few post-choledochojejunostomy ulcers which are not controlled medically—is that occasional operative session untenable if pancreatitis can be frequently controlled by choledochojejunostomy?

Unlike the experience in the experimental animal, the ulcer-appearing incidence must be so low in the human patient that the operation choledochojejunostomy should not be disallowed for this reason.

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Carcinoid (Argentaffin) Tumors of the Gastrointestinal Tract

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Carcinoid tumors of the gastrointestinal tract have received more attention in the literature than the frequency of their occurrence would justify. This is, no doubt, because of the unusual clinical and pathological characteristics of these tumors. The origin of the carcinoid tumors has been the subject of much controversy in the past. The malignancy potential of these tumors has not been fully appreciated.

We have reviewed all of the cases of carcinoid tumors in the pathological files of St. Luke's Hospital, Chicago. We wish to emphasize the malignancy potential of these tumors.

Historical Review

Langhans [1] described what was undoubtedly a carcinoid of the small bowel, in 1867, although he did not recognize it as such. Lubarsch [2] has usually been credited as the first to describe a carcinoid tumor. In 1882, he described a tumor of the ileum which differed from the usual carcinoma of the bowel. He noted the multicentric origin, the lack of gland formation, the cellular dissimilarity to adenocarcinoma, and the slighter tendency to metastasize. He still believed, however, that these tumors were true carcinomas, and in a later article [3] he called them "little carcinomas."

Oberndorfer [4] discussed these tumors in 1907, at which time he first used the term "carcinoid," which term means a tumor resembling a carcinoma. He did not consider them to be malignant, even though they resembled carcinomas in many respects. Huebschmann [5] in 1910 suggested that these tumors might arise from chromaffin cells. Aschoff [6] called them "mucous membrane naevi," which is a good connotation, for they do resemble a nevus somewhat in histological appearance and have their origin from basigranular layers, as do the nevi. He recognized their potential malignancy. Krompecher [7] pointed out the resemblance of these tumors to basal-cell carcinomas of the skin, a point which Banting [8] had made at an earlier date. Saltykow [9] in 1912 suggested that these tumors originate from pancreatic islet-cell rests, because of the cellular similarity. Certain bronchial adenomas, called "carcinoid variants," also closely resemble the carcinoids of the gastrointestinal tract. The slow growth of these bronchial adenomas, the low incidence of metastasis, and the morphological resemblance to the carcinoids is striking.[10] Lewis and Geschichter [11] considered carcinoid tumors to be paragangliomas, originating in the neuroectoderm and migrating in the embryo to the celiac ganglia and thence along the nerve roots to the bowel wall to nerve plexuses beneath the mucosa.

Gosset and Masson [12] and Masson [13] applied the term "argentaffine" to these tumors because there were granules within the cells, which took a silver stain. They postulated their origin from enterochrome, chromaffin cells, the so-called Kulchitsky cells of the basigranular layer of the crypts of Lieberkühn of the gastrointestinal tract. Stout,[14] however, showed that many of these tumors, especially those of the rectum and

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colon, had cells that did not take a silver stain. He suggested that they arose from Erspamer's preenterochrome cells, which are the precursors of the Kulchitsky cells of the crypts of Lieberkühn.

It is now generally accepted that carcinoid tumors arise from the Kulchitsky cells of the crypts of Lieberkühn of the gastrointestinal tract. They should, then, be found anywhere in the gastrointestinal tract where these cells occur. Carcinoid tumors have been reported as occurring in the stomach,* gall bladder,† duodenum,‡ small bowel,§ Meckel's diverticulum,‖ appendix,¶ ileocecal valve,# cecum,** colon,†† rectum,‡‡ and in the gastrointestinal components of teratomas of the ovary.§§

Incidence

In this series of 51 carcinoid tumors from the pathological files of St. Luke's Hospital, 74.5% were appendiceal in location (Table 1). Pearson and Fitzgerald reported an incidence of occurrence at the Boston City Hospital of 28 in 47,479 surgical specimens and 38 extra-appendiceal carcinoids in 11,621 autopsies. Ninety-seven per cent of their carcinoids occurred in the appendiceal area. These tumors may be found at any age. The youngest reported case in the literature was that of an infant of 10 days with a small-bowel carcinoid.[35]

Kulchitsky cells are most numerous in the duodenum, yet peculiarly enough carcinoid tumors of the duodenum are rare. In the small bowel they occur more frequently. According to Dockerty and co-workers,[36] carcinoid tumors comprise 23% of all small bowel tumors. They are multiple in one-third of the small bowel cases. As many as 68 discrete tumors have been reported in one small bowel specimen.[40] Carcinoids of the small bowel usually occur in the ileum, in contrast to carcinomas, which are more prone to develop in the jejunum. Carcinoids of the colon and rectum are less frequent in occurrence. Mayo and McKee in 1950[96] were able to collect only 64 reported cases of rectal carcinoids from the literature, to which they added two cases of their own. Since then there have been a large number of rectal carcinoids reported,‖ bringing the total to 130 cases, including the four cases in our series. Rectal carcinoids may be multiple, but they are more frequently single.

TABLE 1.—*Carcinoid Tumors of the Gastrointestinal Tract from the Pathological Files of St. Luke's Hospital, Chicago*

Location	Cases, No.	Metastasis
Appendiceal	38	No metastases
Cecal	1	Metastases
Small bowel	5	4 with metastases
Rectosigmoid	1	No metastases
Rectum	4	No metastases
Carcinoid of the spermatic cord	1	Probably this was a metastasis
Carcinoid of liver	1	Metastases
Total	51	7 metastases

* References 15-22, 109.

† References 23-25.

‡ References 26-30, 109.

§ References 22, 29-67, 108, 109.

‖ References 29, 68-73.

¶ References 11-13, 16, 19, 20, 22, 24, 27, 29, 30, 34, 39, 59, 80, 83, 90, 98-106, 109.

References 28, 32, 36, 41, 74-79.

** References 9, 19, 20, 24, 29, 30, 35, 36, 59, 77, 81-90, 107.

†† References 16, 30, 59, 77.

‡‡ References 22, 30, 91, 92, 109.

§§ References 93 and 95.

Clinical and Pathological Characteristics

Grossly, carcinoid tumors are light yellow in color, probably owing to the high lipoid content. They are usually antimesenteric and submucosal in location in the bowel wall. The typical cell is a small epithelial cell with an oval or round nucleus that has a well-defined nuclear membrane and a fine stippling of chromatin. The cytoplasm is palely acidophilic, small in amount, vacuolated or granular. The cells are in columns, nests, coils, or masses. In the rectum they may take the form of coiled festoons or ribbons.

Tumor cells in the metastatic foci may look benign by the usual histological criteria of malignancy. Frequently the cells in the metastatic deposit may take on an entirely

‖ References 22, 30, 91, 92, 108, 109.

different histological arrangement than that seen in the primary tumor.

The small-bowel carcinoids may manifest themselves by an acute obstruction due to intussusception of a polypoid tumor, as in the following case.

CASE 1.—*Small Bowel Carcinoid with Intussusception.*—A 44-year-old Negro man entered St. Luke's Hospital March 5, 1951, with a history of pain, nausea, and emesis of three day's duration. The pain was in the epigastrium and the right lower quadrant of the abdomen. The clinical diagnosis was acute appendicitis. He was operated upon by Dr. H. E. Mock Jr. An ileocolic intussusception was found, and a right colon resection was done including 36 cm. of ileum. The specimen showed a polypoid tumor in the wall of the bowel 24 cm. from the ileocecal valve, with about 30 cm. of ileum invaginated through the ileocecal valve and incarcerated in the cecum and ascending colon. This polypoid tumor was a carcinoid (Figs. 1 and 2). There were no metastatic nodes involved.

Fig. 1 (Case 1).—Carcinoid tumor of the ileum which produced intussusception and obstruction.

Obstruction by intussusception in carcinoids of the small bowel has been reported by Bowers and Cheek,[65] Mufson and Horowitz,[103] Jones,[104] Ariel,[32] and McGlannan.[105]

Carcinoid tumors may obstruct the wall of the small bowel by knuckling and metastases, as shown in the following case.

CASE 2.—A white man of 53 years entered St. Luke's Hospital May 22, 1950, on the Service of Dr. Will F. Lyon. His complaints were cramps in the stomach and low back pain of 10 months' duration. At the time of onset of the complaints, he had generalized cramps with nausea and vomiting for a 24-hour period. He felt weak afterward and did not return to work for two months. His stools were on occasion liquid. Three months later a similar attack occurred and lasted eight weeks. Three weeks prior to the time of his admission he had a similar third attack. Low back pain relieved by the passage of gas was a prominent symptom. Weight loss was 30 lb.

At the time of admission the abdomen was tense, tympanitic, and doughy. The red blood cell count was 3,200,000 cells per cubic millimeter, and the hemoglobin level was 6 gm. X-rays suggested a small bowel obstruction. At operation a tumor of the small bowel with extensive retroperitoneal me-

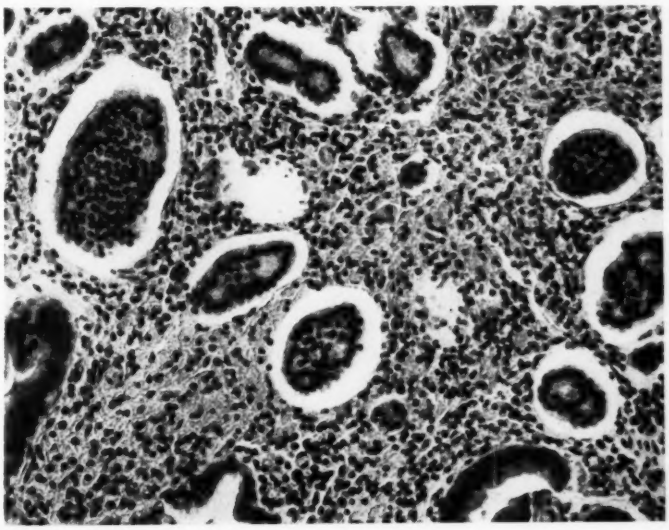

Fig. 2 (Case 1).—Photomicrograph of carcinoid tumor of the ileum.

tastases was found. The patient died 37 days after admission. (The specimen is shown in Fig. 3 and Fig. 4.)

This case was one of two small-bowel carcinoid tumors with metastases reported by Dangremond in 1942.[33] It is included here again, with the permission of the journal and author, because it so well illustrates the knuckling of the bowel and obstruction which occurs owing to extensive growth along one side of the bowel wall. The other case reported by Dangremond was a small-bowel carcinoid with mesenteric node metastases coincidentally found on autopsy in an elderly man who died of a urinary tract lesion.

Small-bowel carcinoids are frequently multiple. The following case is an example of this.

CASE 3.—*Multiple Small Bowel Carcinoids with Metastases.*—A 45-year-old white woman was hospitalized three times prior to August, 1948. On the first occasion a nephrectomy had been done for pyelonephritis secondary to a staghorn calculus.

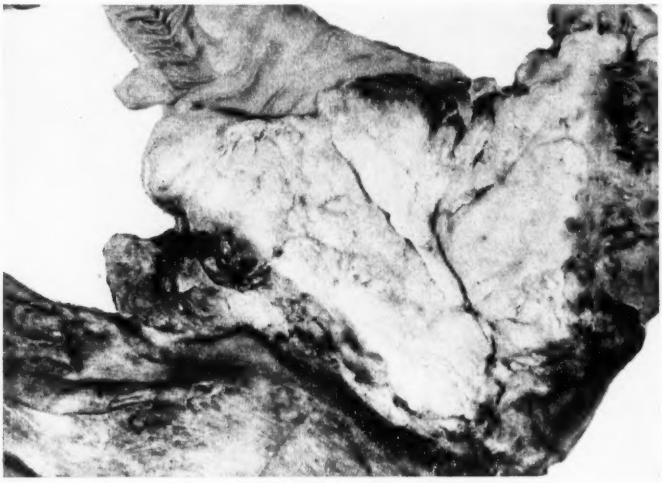

Fig. 3 (Case 2).—Carcinoid tumor of the ileum producing obstruction by growth along one wall with kinking. (Courtesy of Dr. Gerritt Dangremond and the *American Journal of Clinical Pathology*, Williams & Wilkins Company, Publishers.)

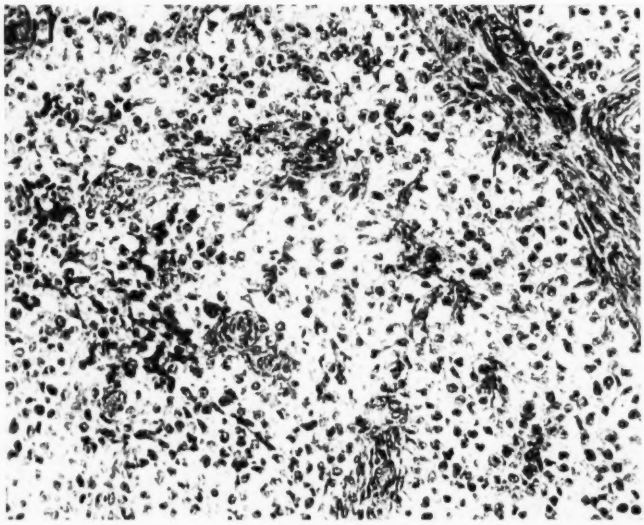

Fig. 4 (Case 2).—Photomicrograph of carcinoid tumor of the ileum. (Courtesy of Dr. Gerritt Dangremond and the *American Journal of Clinical Pathology*, Williams & Wilkins Company, Publishers.)

On the second admission a vaginal hysterectomy was done. Nine months after the hysterectomy she was again admitted, because of left flank pain. Orthopedic, urological, and gastrointestinal tract studies and consultation were negative. The complaints persisted, and she was again hospitalized after a period of four months. During this latter hospital stay, she developed nausea, vomiting, and localization of the pain to the left lower abdomen. X-ray studies of the small bowel showed a moderately dilated lower ileum with some areas of segmental spasm. At operation multiple carcinoid tumors of the lower ileum were found. A long segment of ileum was resected. This showed metastatic nodes in the mesentery (Figs. 5 and 6). No liver metastases were noted. This patient developed a recurrence in two years' time, was reoperated on, and had additional bowel and mesentery removed.

This case was previously reported in a study of small-bowel tumors by Strohl, Diffenbaugh, and Sarver, in 1951.[66] It is included here to illustrate the multiple lesions frequently present in carcinoid tumors of the small bowel. Occasionally, carcinoid tumors of the bowel may spread by way of the portal venous tributaries directly to the liver with no lymph node involvement. Huge metastases may occur in the liver.

Thorson and co-workers[110] recently called attention to the association of liver metastases from carcinoid tumors of the small bowel with cyanosis, peripheral vasomotor symptoms, pulmonic stenosis, and tricuspid regurgitation without septal defects. They reported seven certain, four probable, and five qualified cases from their own experience and from the continental literature. They suggested that the vascular lesions were acquired, being secondary to the prolonged action of serotonin, secreted by the tumor tissue. That carcinoid tumors may be functioning neurocrine tumors related to

Fig. 5 (Case 3).—Multiple carcinoid tumors of the small bowel. (Courtesy of Dr. E. Lee Strohl and *Surgery, Gynecology and Obstetrics,* Surgery Publishing Company of Chicago, Publishers.)

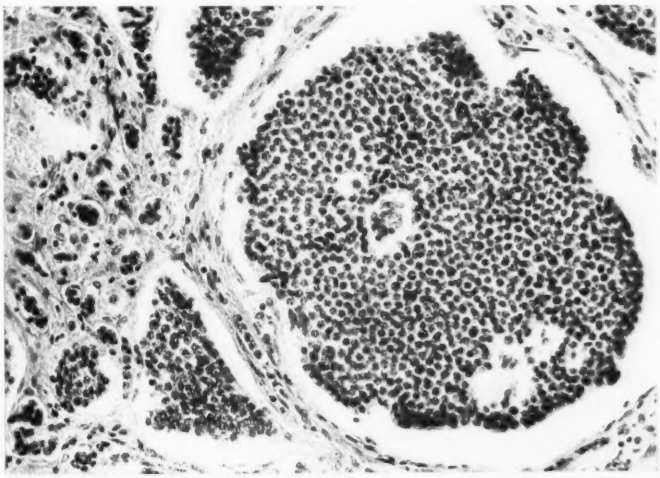

Fig. 6 (Case 3).—Photomicrograph of mesenteric lymph node metastases. (Courtesy of Dr. E. Lee Strohl and *Surgery, Gynecology and Obstetrics,* Surgery Publishing Company of Chicago, Publishers.)

pheochromocytomas has been suggested occasionally in the literature.¶ The isolation of 5-hydroxytryptomine from a carcinoid tumor by Lembeck [111] lends credence to this possibility.

The following case is similar to those reported by Thorson. The patient was extensively studied by our cardiovascular research department. The full detailed report will be reported by them later.

Case 4.—A 53-year-old woman first entered St. Luke's Hospital in March, 1954, with a history of dyspnea and edema of the abdomen and legs of five months' duration. Cardiac catheterization was carried out, as well as many other laboratory procedures. The clinical diagnosis was congenital heart disease with pulmonic stenosis, relative tricuspid insufficiency, and interatrial septal defect with right to left shunt. The edema responded to diuretics.

She was hospitalized again in June, 1954, because of weakness, fatigue, lower abdominal distress, nausea, and emesis. A mild diarrhea was present. A mass palpable in the right upper quadrant was considered to be an enlarged liver. The red blood cell count was 3,800,000/cu. mm., with 10.8 gm. of hemoglobin. Gastrointestinal x-rays were negative. Pyelograms showed a double right kidney and ureter.

The third hospitalization occurred in September at which time there was marked dyspnea, edema, palpitation, fatigue, and weakness.

¶ References 111 and 112.

Her final hospitalization was in April, 1955, because of cyanosis, weakness, and tremendous edema. Death occurred May 3, 1955. Autopsy disclosed the carcinoid of the terminal ileum with extensive metastases to the liver, pulmonic stenosis, and tricuspid stenosis without atrial septal defect (Figs. 7, 8, 9, and 10).

This patient showed the peculiar flushing and cyanosis of the skin described by Thorson.

Small carcinoid tumors of the ileocecal valve and cecum produce few symptoms and bleed rarely, because they are submucosal in location. Only 34 cases of carcinoids in this location have been reported in the literature. The percentage of metastases has been 81%. The following case illustrates such a lesion.

Case 5.—*Cecal Carcinoid with Metastases.*—A 68-year-old man entered St. Luke's Hospital in June, 1947, on the surgical service of Dr. Guy V. Pontius. He gave a history of anorexia, emesis, and weight loss of 40 lb. There was a history of occasional diarrhea over a period of three years. There had been blood in his stool in July, 1946, before a suprapubic prostatectomy and hemorrhoidectomy had been performed. However, no gastrointestinal studies had been done at that time. At the time of the last admission, a fixed mass was present in the area of the hepatic flexure of the colon. Barium studies with x-ray showed a high cecum but no evidence of a filling defect. The clinical diagnosis was cirrhosis of the liver with heart

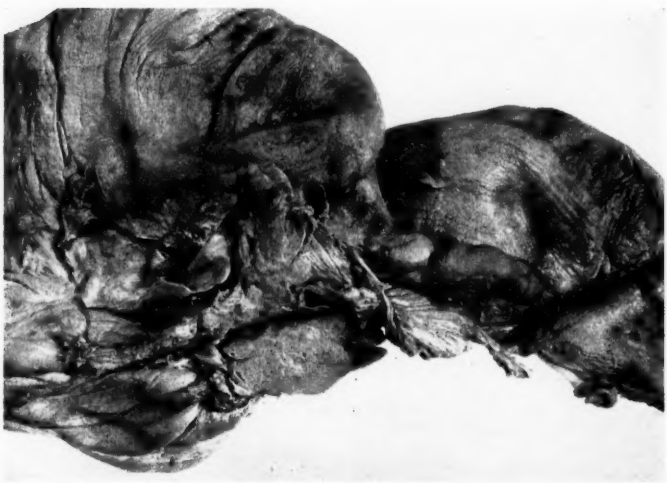

Fig. 7 (Case 4).—Carcinoid tumor of the terminal ileum just at its entrance into the cecum. (Tumor tissue is in the lower center of the picture.)

disease, with the possibility expressed that this might be a hepatoma. The patient refused exploration. Death occurred in July, 1947. Autopsy showed a carcinoid tumor of the cecum with metastases to the liver and regional nodes (Figs. 12, 13, and 14.)

Carcinoid tumors elsewhere in the colon have been reported infrequently. Only six previous colon carcinoids have been reported. The following case report is of interest because of the differential diagnosis of diverticulitis.

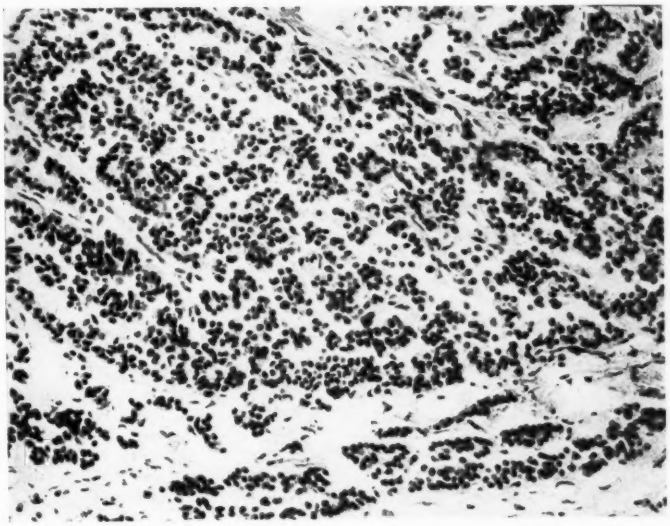

Fig. 8 (Case 4).—Photomicrograph of the carcinoid tumor of the ileum in figure 7.

Fig. 9 (Case 4).—Liver metastases from the carcinoid tumor of the ileum in Figure 7.

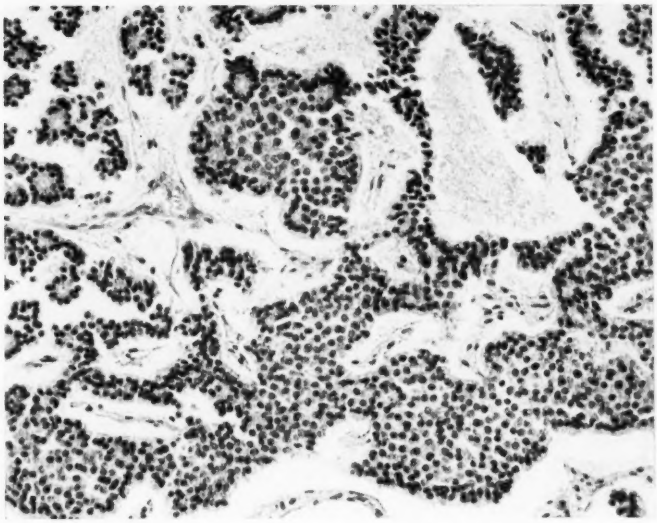

Fig. 10 (Case 4).—Photomicrograph of the carcinoid deposits in the liver in Figure 9.

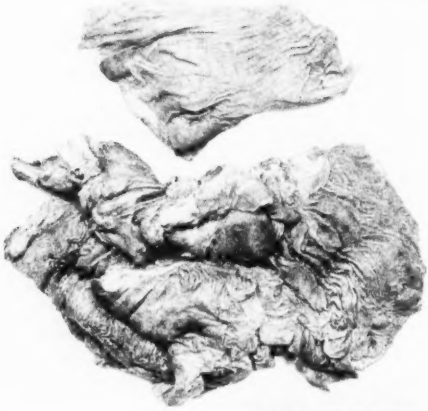

Fig. 11 (Case 5).—Carcinoid tumor of the cecum with metastases.

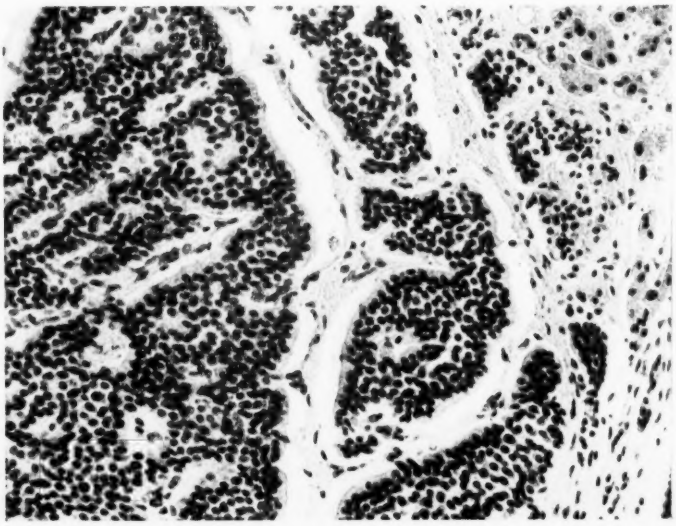

Fig. 12 (Case 5).—Photomicrograph of the carcinoid of the cecum in Figure 11.

Fig. 13 (Case 5).—Liver metastases from the carcinoid of the cecum in Figure 11.

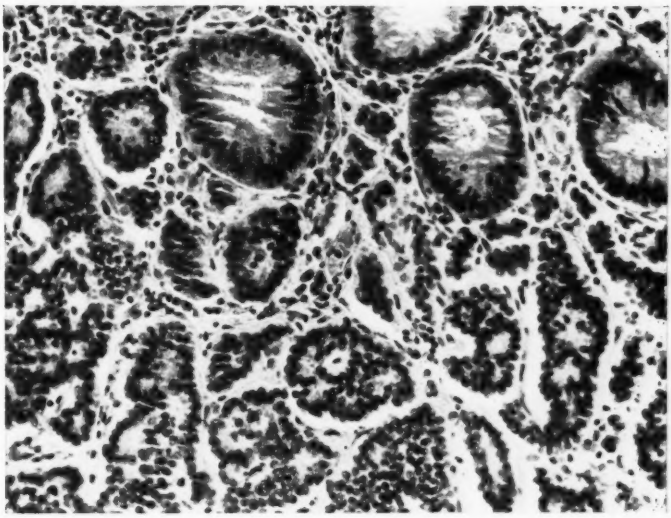

Fig. 14 (Case 6).—Photomicrograph of a carcinoid of the sigmoid along with the diverticulitis.

CASE 6.—*Carcinoid of the Sigmoid Colon.*—A 55-year-old white man entered St. Luke's Hospital May 14, 1951, with a complaint of lower abdominal pain and obstipation of several weeks' duration. A previous urinary tract infection had presented symptoms of similar nature, and so the patient had interpreted these later symptoms as to a recurrence of his previous trouble. There was no nausea, vomiting, or weight loss. There was a palpable abdominal mass in the left lower quadrant. X-ray revealed an obstructing lesion in the sigmoid colon, believed to be a diverticulitis with perforation. The patient was placed on a conservative regimen with antibiotics, but the mass failed to resolve. The patient had a septic temperature throughout the hospital stay. The red blood cell count was 3,900,000/cu. mm.

On May 31, 1951, after preparation with succinylsulfathiazole (Sulfasuxidine), the patient was operated upon by Dr. Guy V. Pontius. An inflammatory mass in the sigmoid colon was found adherent to the left ureter and pelvic brim. No evidence was present of proximal spread. A wide resection was done, with end-to-end approximation of the colon. The specimen showed both diverticulitis and carcinoid tumor. There were no involved metastatic nodes, although the tumor had invaded the wall of the bowel. The patient made a slow, but uneventful, recovery and shows no evidence of recurrence four years after surgery.

Carcinoma as well as carcinoid may be masked by an apparent diverticulitis of the sigmoid colon.

Rectal carcinoids are usually small, sessile, polypoid tumors found on routine sigmoidoscopic examination or at the time of minor rectal operations. This was the case in the four patients with rectal carcinoids in this series.

Case 7.—*Carcinoid of the Rectum.*—A 70-year-old physician was referred to Dr. Foster L. McMillan on Sept. 28, 1951, for a sigmoidoscopic examination as part of a general physical work-up. The patient was having no gastrointestinal complaints at the time of the examination. On the posterior wall of the rectal ampulla, approximately 10 to 12 cm. from the anal outlet, a small polypoid lesion was found. A biopsy specimen was taken from the lesion, and then the base was thoroughly desiccated with the fulgurating electrode. The microscopic diagnosis was carcinoid tumor. Careful follow-up examinations have shown no evidence of recurrence.

Case 8.—*Carcinoid of the Rectum.*—A 29-year-old Negro truck driver was admitted to St. Luke's Hospital June 15, 1952, with a history of rectal bleeding of several months' duration. Internal and external hemorrhoids were present and also a palpable, pedunculated, 1×1 cm. mass just above the anal outlet on the anterior rectal wall. A barium enema was negative. No other lesion was seen on sigmoidoscopic examination. Hemorrhoidectomy and local wide excision of the tumor was carried out by Dr. L. J. Witkowski. The pathological diagnosis was carcinoid. There has been no evidence of recurrence to date.

Case 9.—*Carcinoid of the Rectum.*—A 57-year-old white woman was operated upon for an adenocarcinoma of the rectosigmoid colon in November, 1951, by Dr. John T. Reynolds. An anterior resection was done. The patient made an uneventful recovery. In the early follow-up examination a sigmoidoscopic observation was done. Just distal to the anastomotic site a very small polypoid tumor was found. This lesion was removed through the sigmoidoscope and the base fulgurated. Microscopic examination by the pathologist revealed a carcinoid. This patient has shown no evidence of recurrence to date.

The fourth rectal carcinoid in this group was found on routine examination in a 51-year-old Negro woman who came to the clinic complaining of anal pruritus. Upon routine sigmoidoscopic examination a small polypoid lesion was found on the anterior rectal wall about 5 cm. from the anal margin. This was excised widely under general anesthesia. This case was reported by one of us (W. G. D.) in 1954.[91] There has been a recent follow-up examination with no evidence of recurrence.

Local excision was done in the majority of the 130 cases of rectal carcinoids reported in the literature (including the four cases reported here). Radical abdominoperineal excision was recorded in 10 of these reported cases. Six of these ten cases were operated upon under the erroneous diagnosis of small-cell carcinoma or anaplastic carcinoma. Three of these resected cases showed metastatic nodes.

Only one recurrence after local excision of a rectal carcinoid has been reported in the literature. Mrazek, Godwin, and Mohardt[29] in 1953 reported a recurrence with hepatic and pulmonary metastases in a 58-year-old man. This occurred 37 months after local excision of a rectal carcinoid.

We believe that most of these small rectal carcinoids are found and removed before metastases occur.

Comment on the Malignancy of these Tumors

Ransom in 1890[97] was the first to report metastases from a carcinoid, which in this case was of the ileum. Since then many additional reports of metastases from these tumors have appeared in the literature. Ritchie and Stafford[39] in a review of 332 carcinoid tumors in 1944 found a 37.9% incidence of metastases.

Metastasis by lymphatic spread is commonest, but there may be vascular invasion with widespread metastases. Portal spread to the liver is not uncommon (Case 4). Metastases have been reported as occurring to the regional nodes, liver, lungs, bones, spleen, kidneys, brain, adrenals, subcutaneous tissue, and testes. The case in this series of a carcinoid nodule in the spermatic cord, found during a varicocele operation, was probably a metastasis. The case was lost to follow-up and had no exploratory laparotomy. Ritchie and Stafford[39] and Ashworth and Wallace[72] mention metastases to the testis.

In a review of the literature we found the incidence of metastases from each area of the gastrointestinal tract to be that given

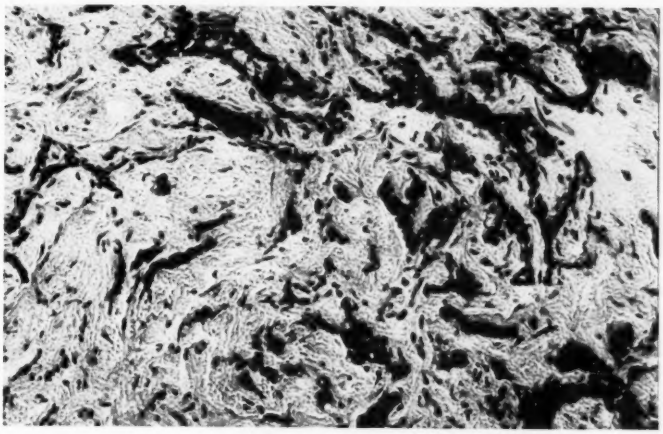

Fig. 15 (Case 7).—Photomicrograph of carcinoid tumor of the rectum.

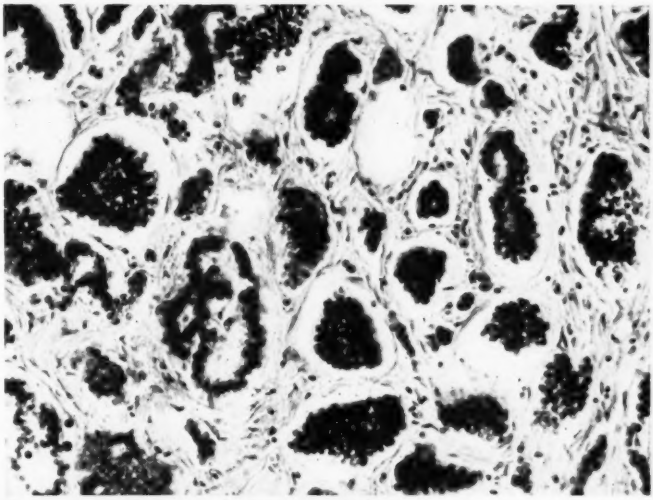

Fig. 16 (Case 8).—Photomicrograph of carcinoid tumor of the rectum.

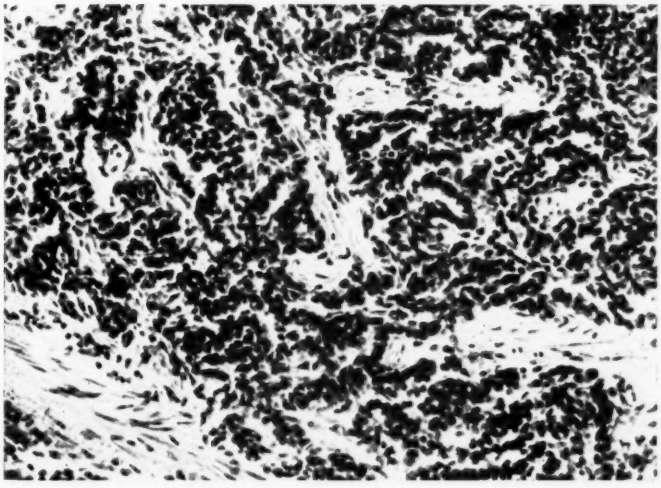

Fig. 17 (Case 9).—Photomicrograph of carcinoid tumor of the rectum.

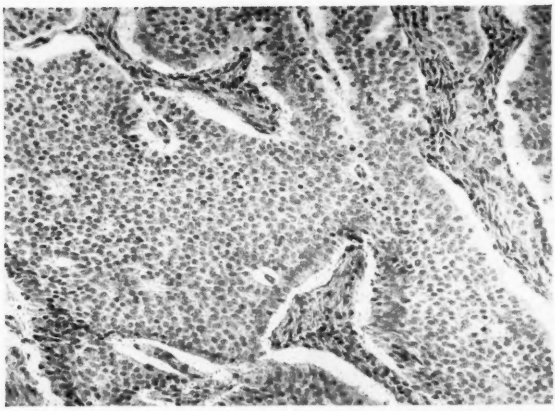

Fig. 18.—Photomicrograph of a carcinoid tumor of the appendix showing the infiltration of the appendiceal wall.

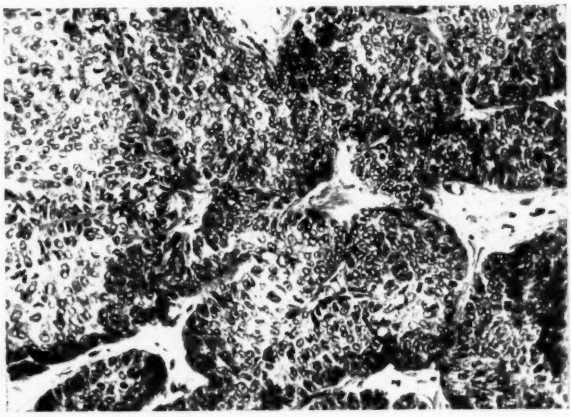

Fig. 19.—Photomicrograph of a carcinoid tumor of the appendix showing invasion of the muscularis and deep layers of the appendiceal wall.

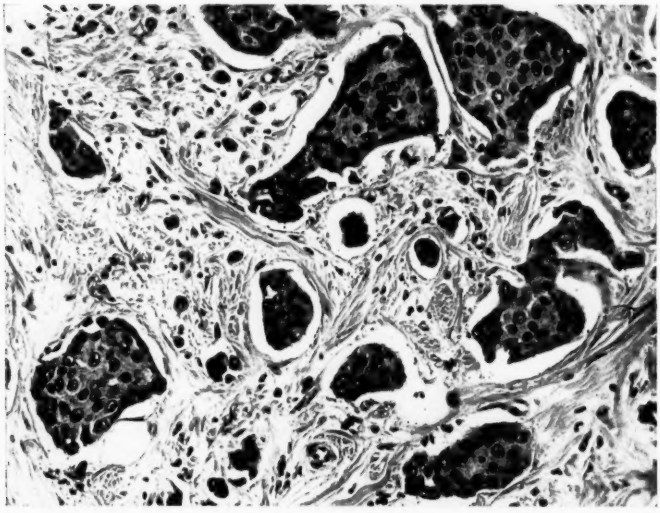

Fig. 20.—Photomicrograph of a carcinoid tumor of the appendix showing infiltration of the layers of the appendiceal wall.

in Table 2. The appendiceal carcinoids have been considered to be clinically benign. Some 29 cases of metastatic spread from appendiceal carcinoids, however, have been reported in the literature.# One of these occurred in a 16-year-old girl.[80]

We believe these tumors all have malignant potential wherever in the gastrointestinal tract they are located. In reviewing the histology of the tumors in this series, we were impressed with the frequency of invasion of the submucosal, muscular, and serosal layers of the appendiceal wall by the carcinoid tumor cells. (Figs. 18, 19, and 20.)

TABLE 2.—*Percentage of Metastases in Carcinoid Tumors from Various Areas of the Gastrointestinal Tract as Reported in the Literature (Includes Cases in the St. Luke's Series)*

Location of Carcinoid	Total Cases	Cases with Metastases	Percentage Metastases
Stomach	29	4	13.7
Gall bladder	4	0	0
Duodenum	21	4	19
Small bowel	438	150	34.2
Appendix	825	29	3.5
Meckel's diverticulum	8	0	0
Ileocecal Valve	13	11	84.6
Cecum	21	16	76.1
Colon	7	3	42.8
Rectum	130	18	13.8

The time factor is probably of importance in explaining the variation in the reported incidence of metastatic spread from carcinoid tumors in different areas of the gastrointestinal tract. This has been mentioned by several writers.* Carcinoid tumors of the appendix are associated with a high incidence of obliterative fibrosis of the appendiceal lumen. These cases have obstructive symptoms and are removed at an early date or are incidentally removed at the time of laparotomy for other disease. Credence is given to this view by the fact that the average age of the patients having removal of appendiceal carcinoids is 25 years, whereas the average age of the patients with small-bowel carcinoids, at the time of their discovery, is 55 years.† Small-bowel carcinoids are frequently multiple, again increasing the percentage possibility of malignancy. Small-bowel tumors of all types produce symptoms at a late date and are difficult to detect, even at x-ray examination. Carcinoids are usually submucosal and do not bleed as frequently as do the carcinomas. These multiple factors could account for the late time of detection of these tumors and the consequent higher incidence of metastases. Small tumors of the cecum and colon would be even more difficult to detect at an early date, as bleeding and obstruction do not, as a rule, occur with these small tumors. Carcinoids of the rectum, on the other hand, are frequently removed at an early date during the course of routine sigmoidoscopy or hemorrhoidectomy. The percentage of cases discovered relatively early is high and that of metastatic spread correspondingly low. Carcinoids of the stomach and duodenum are usually removed in specimens resected for another disease. Only 10 of the 28 carcinoids of the stomach reported in the literature produced symptoms.

References 23, 29, 30, 60, 90, 98-102.

* References 24, 32, and 80.

† References 80 and 100.

Summary

The clinical and pathological findings of carcinoid tumors of the gastrointestinal tract from available pathological material at St. Luke's Hospital and from reported cases in the literature are reviewed.

This type of tumor can appear anywhere along the gastrointestinal tract from stomach to anus.

Review of the histology of the appendiceal carcinoids shows frequency of invasion of the muscle and serosal layers of the appendix, even though evidence of lymph-node metastases is infrequent.

It is our belief that this type of tumor, wherever located, is malignant. The incidence of metastases of these tumors in various areas of the gastrointestinal tract usually parallels the stage in time at which the tumor is detected.

Dr. Edwin F. Hirsch, Director of the Henry Baird Favill Laboratories at St. Luke's Hospital, helped in organizing this material and in providing the photographs and photomicrographs.

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Thrombin-Fibrinogen Coagulum as a Nonsuture Method of Nerve Anastomosis

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Certain unsatisfactory features associated with the use of sutures in the conventional methods of apposing nerve ends have stimulated efforts to find better techniques for nerve anastomoses. Young and Medawar [1] introduced a nonsuture method of peripheral nerve anastomosis using fortified cockerel plasma with chick embryo extract as a "glue" between the nerve ends in rabbits. This technique was also used by Seddon and Medawar [2] with a human median nerve. Tarlov and Benjamin [3] repeated these experiments and found considerable reaction and fibrosis with the use of cockerel plasma and chick embryo extract. As a result, they evolved a more satisfactory method of plasma-clot suture using autologous plasma with autologous muscle extract. Subsequently, a rather elaborate technique was developed * using plastic molds of various sizes to contain temporarily the plasma clot in its formative stage.

Because of the tendency for nerve ends united by the plasma clot to separate if approximated under tension, fine tantalum wire nerve sutures were placed, in addition, some distance on either side of the anastomoses.[5] Bateman [9] used two nonabsorbable surgical (silk) nerve sutures to relieve tension on the plasma clot anastomosis and reported satisfactory results with this modification in more than 350 human cases. Klemme and his associates [10] published encouraging results in a small number of human cases with a modified technique using acacia as the glue.

The encouraging results † noted in our experiments with broad applications of a coagulum made from thrombin ‡ and fibrinogen § stimulated this study using the coagulum as a nonsuture method of nerve anastomosis. Tarlov [5] mentioned the use of fibrinogen and thrombin but found that the clots underwent a variable degree of lysis after 24 to 48 hours, allowing the nerve ends to separate. No further work was reported with thrombin and fibrinogen clots for this reason. In vitro studies here ‖ have shown no significant degree of lysis with the use of the present thrombin and fibrinogen preparations. Therefore, a controlled study was undertaken in dogs, and the results, as determined by repeated nerve regeneration tests with comparative morphologic examinations, will be described.

Procedure

Thrombin and Fibrinogen.—The problem of having excess fluid (serum) following the conversion of fibrinogen to fibrin was present when plasma was used as a source of fibrinogen. Purified fibrinogen was chosen to eliminate this feature. Our in vitro studies showed the tensile strength of the coagulum to be directly proportional to the concentration of the fibrinogen as well as the thrombin. Because the desiccated fibrinogen used in this study was by nature difficult to dissolve in

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* References 4 through 8.

† Unpublished data.

‡ Thrombin, topical (bovine origin). Each vial contains 5000 N.I.H. units of sterile dried thrombin. Supplied by Parke, Davis & Company.

§ Each vial contains 1 gm. of sterile, dried fibrinogen (Parenogen) prepared from normal human plasma. Supplied by Cutter Laboratories.

‖ Performed by Pvt. David S. Swanson.

a small volume of water or saline, a method was devised for using the fibrinogen in powdered form. In this way it was possible to obtain a concentrated collection of fibrinogen devoid of excess fluid.

The powdered fibrinogen was prepared by soaking the vial containing the lyophilized fibrinogen under refrigerated benzalkonium (Zephiran) chloride solution for several days. Then, under sterile conditions, the bottle was dried and the cap removed. Sterile glass beads were placed in the vial and the vial opening covered with a disc of copper screen. A rubber bottle cap with the top partially cut away was placed over the screen. This opening was kept covered at all times, except during use, by a finger cot. The vial was wrapped in a sterile towel and placed in a mechanical shaker until the fibrinogen was entirely in powdered form.

Fig. 1*A*. — Photograph of dog sciatic nerve taken at operation. Severed nerve ends retracted 12 mm., oilcloth strip placed in nerve bed.

Thereafter, it was kept in a refrigerator and brought out only during times of use. During use, the fibrinogen powder was expressed from the vial in a manner similar to shaking the contents from a salt shaker. Repeated tests have shown no evidence of deterioration or bacteriologic contamination provided the precautions were strictly observed.

Thrombin was used mostly in a concentration of 2000 N.I.H. units per cubic centimeter (5000 N.I.H. units per vial dissolved in 2.5 cc. isotonic saline). More concentrated solutions of thrombin were made, but this concentration was believed to be adequate for the demands of this study.

Method.—Adult mongrel dogs with an average weight of 25 lb. were used. Intravenous pentobarbitol (Nembutal) was employed as the anesthetic. The skin was shaved and carefully prepared with thimerosal (Merthiolate) solution. Rigidly sterile technique was used throughout. The sciatic nerve was carefully exposed and freed through a muscle-splitting incision over the lateral aspect of the lower buttock and thigh. Accurate hemostasis was demanded, and all undue trauma was avoided. The sciatic nerve was cleanly divided with a sharp new knife blade at a standard site. This site varied with the size of the dog, but it averaged about 5 cm. from the exit of the sciatic nerve from the pelvis. Bleeding from the cut nerve ends was usually controlled by gentle sponge pressure. The cut nerve ends retracted from 0.5 to 4.0 cm., with an average of 1.0 to 1.5 cm. (Fig. 1*A*).

A narrow strip of sterile oilcloth was placed as a trough in the nerve bed (Fig. 1*B*). After complete hemostasis, the epineurium of the retracted nerve ends was gently grasped with fine iris forceps and the ends were partially approximated. Several drops of thrombin were then placed between the nerve ends. A small amount of fibrinogen powder, which had been deposited previously in a sterile paper cone, was carefully sprinkled over the end of each nerve stump by lightly tapping the paper or using a probe. The two nerve ends were then closely approximated and held in that position for a period varying from one-half to four minutes, depending upon the distance the cut nerve ends had retracted initially. Occasionally, it was helpful to add an additional amount of powdered fibrinogen and thrombin solution around the anastomosis. The small arteries on the nerve surface served as useful landmarks in obtaining accurate alignment of the nerve ends. Separation of the nerve ends seldom occurred after release of the forceps; however, if the nerve ends did separate, the coagulum could be gently wiped free

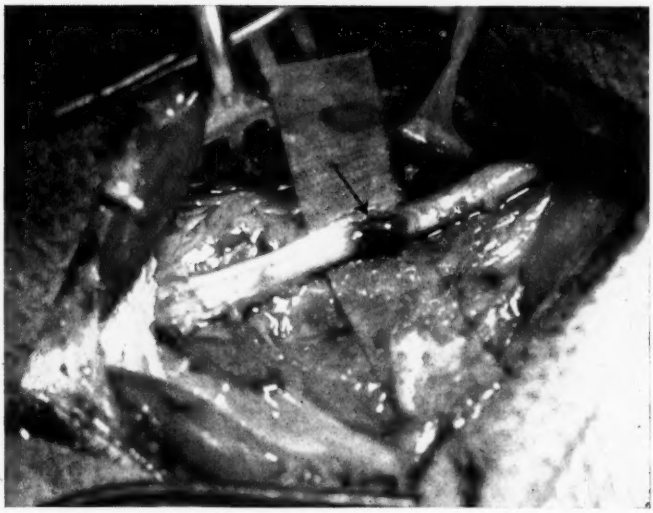

Fig. 1*B*.—Same as Figure 1*A*. Arrow points to thrombin-fibrinogen coagulum anastomosis. Nerve ends remain approximated in freshly formed coagulum.

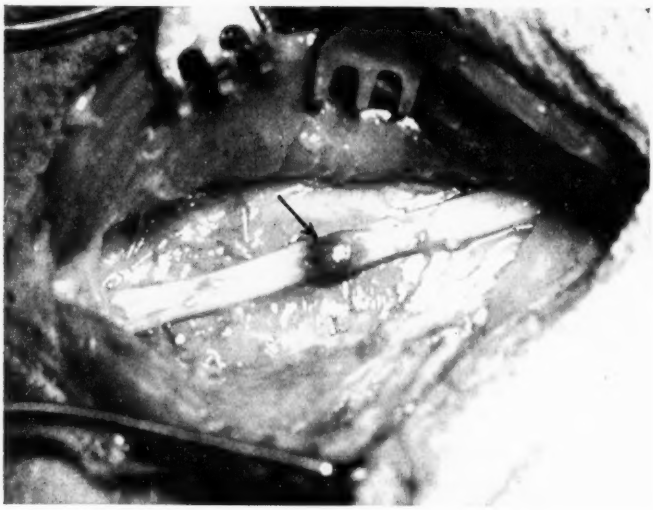

Fig. 1*C*.—Same as Figure 1*A*. Oilcloth strip removed, final appearance of coagulum anastomosis before incision was closed.

and a new one formed with a heavier concentration of fibrinogen. This held the ends in apposition. The oilcloth strip was then easily slid out from under the anastomosis, and any excess thrombin or fibrinogen in the area was lightly sponged away (Fig. 1*C*). The wounds were closed in a uniform manner with interrupted silk sutures.

For control studies, the procedure for exposure and handling of the sciatic nerve in the opposite leg was the same. The nerve was divided at the same site and meticulously approximated by four equally spaced 000000 Atraumatic arterial silk sutures. Efforts were made to grasp only the epineurium and to obtain accurate alignment under proper tension.

Experiments.—A pilot group of eight dogs had unilateral nonsuture sciatic nerve anastomoses with the thrombin-fibrinogen coagulum. These animals were killed at approximately one- to two-day intervals. This showed that the technique was satisfactory without any need for splinting or immobilizing the dog's leg postoperatively.

A group of 30 dogs was next subjected to bilateral sciatic nerve division. One nerve was anastomosed without sutures, with use of the thrombin-fibrinogen coagulum, and the other was

anastomosed with silk sutures and no coagulum, by the techniques described. All animals were given intramuscular penicillin postoperatively and were allowed free movement without any immobilization of the extremities. The dogs were electively killed at 1, 3, 5, 7, 10, and 14 days and the third and fourth weeks postoperatively. Thereafter, they were autopsied at two-week intervals up to eight months.

At the time of autopsy, the operative area was reopened and the nerve and surrounding area were carefully examined. Photographs were taken, and the entire nerve was placed in 10% formaldehyde solution (Formalin). Cross sections of the nerve trunk were examined histologically in all specimens at sites roughly 1 cm. proximal and 1 cm. distal to the anastomosis and at the site of the distal sciatic bifurcation. Longitudinal sections were also taken through the anastomosis. The specimens were stained with hematoxylin and eosin and osmic acid.

A final group of seven dogs had bilateral sciatic-nerve anastomoses as described above. In this group, however, the fibrinogen was prepared as a concentrated solution (1 gm. of lyophilized fibrinogen dissolved in 20 cc. of isotonic saline—a concentration of 0.05 gm/cc.). The coagulum was formed by adding several drops of the fibrinogen solution to the thrombin and apposing the nerve ends in the resulting coagulum. The dogs were electively autopsied at 2, 4, 6, 8, 12, 16, and 20 weeks postoperatively.

Nerve Regeneration Tests

1. *Electromyography.*—The method of electromyography used was based upon that described by Huddleston and associates [11] and Denny-Brown.[12] By introducing a fine needle into a muscle, electrical disturbances secondary to the process of depolarization associated with muscle fiber contraction are transmitted to a visual screen and loud speaker. Thirteen dogs were selected for testing bilateral nerve regeneration at representative intervals up to eight months postoperatively. Two limitations to the method prompted the use of electrodiagnostic testing for the remaining studies: Voluntary contractions obviously were not obtained in the dog, and the time necessary to perform the test thoroughly was excessive.

2. *Electrodiagnostic Testing.*—The technique used was based upon that described by Goldseth.[13] With this method surface electrodes were used with galvanic current, which proved to be less time-consuming and eliminated the need for voluntary muscle contraction. Twenty-one dogs were repeatedly studied at monthly intervals by this method for periods up to eight months; ten dogs had had earlier studies with electromyography.

Results

Both animal and in vitro experiments showed that the coagulum formed from thrombin solution and fibrinogen in powdered form had the greatest tensile strength. The adhesive coagulum formed rapidly, and in instances in which the ends retracted 1 cm. or less upon initial division of the nerve the coagulum had sufficient strength in less than one minute to hold the ends in apposition. When the nerve ends retracted more than 1 cm., it frequently was necessary to hold the ends together in the forming coagulum for periods varying up to three or four minutes. Occasionally, because of poor positioning or slight separation, the newly formed coagulum was purposely wiped away and a new coagulum was made. A heavier concentration of fibrinogen powder was used if there was a tendency for the nerve ends to separate. This effectively counteracted the increased tension. In several instances with extreme retraction, the nerve ends initially separated several millimeters in the coagulum after the forceps were relased, leaving adhesive coagulum stretched between the two ends like a prosthetic bridge. These were purposely left with this separation, and later studies showed that the nerve elements effectively bridged the gap.

The method of performing the anastomosis by holding the nerve ends together in the coagulum contained in an oilcloth trough worked satisfactorily. When the coagulum had formed, the oilcloth strip was easily teased free from beneath the overlying nerve anastomosis. It was not felt necessary to use preformed cups or molds for this purpose; however, it was important to sponge away any excess thrombin or fibrinogen that occasionally spilled beyond the confines of the oilcloth.

Persistent bleeding from the severed nerve ends was a problem occasionally. If this was not adequately controlled, a hematoma would form that was contained by the coagulum. When this occurred, both coagulum and hematoma were wiped away,

the bleeding was controlled, and the nerve ends were reanastomosed by a newly formed coagulum.

There was no instance of infection or wound breakdown. A number of dogs developed postoperative foot-drop and had to have padded stockings to protect the denervated distal extremities from inadvertent trauma during movements around the cage. In several, areas of peripheral necrosis developed, but these apparently caused no pain or distress.

In all instances, except one in which a strip of loose muscle accidentally became interposed, the nerve ends remained in apposition with the use of the coagulum and no sutures. Even though in apposition, the nerve ends could be pulled apart with moderate traction at autopsy for the first five days. Thereafter, the ends became more firmly united and the nerve could be handled and sectioned without separation. In almost every instance comparison of the two sides showed the coagulum anastomoses to be somewhat less bulky with less fibrous reaction than the control ones, with silk sutures (Fig. 2). In fact, we gained the impression that the coagulum formed a pseudoprotective coat about the anastomosis, allowing free crossing of nerve elements but minimal infiltration of adjacent fibrous tissue.

On histologic examination the coagulum could be identified during the early period as a homogeneous pink substance that was undergoing acute polymorphonuclear leucocytic infiltration. By the end of the first week the inflammatory reaction had increased but had shifted to a more chronic phase, including the presence of histiocytes and macrophages. Along with the vascular fibroblastic proliferation, neurilemmal

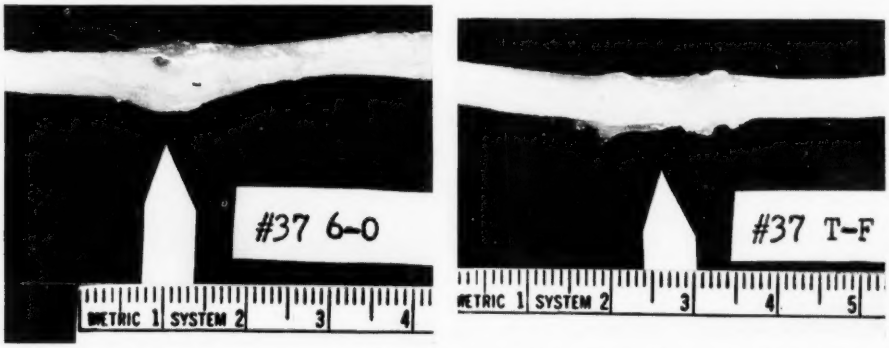

Fig. 2*A*.—Photographs of dog sciatic nerves removed at autopsy. Nerves on left anastomosed with 000000 silk; those on right, with thrombin-fibrinogen (*T-F*) coagulum. Arrow points to site of anastomosis. Note more bulbous appearance of anastomoses with silk. Photographs taken at four weeks.

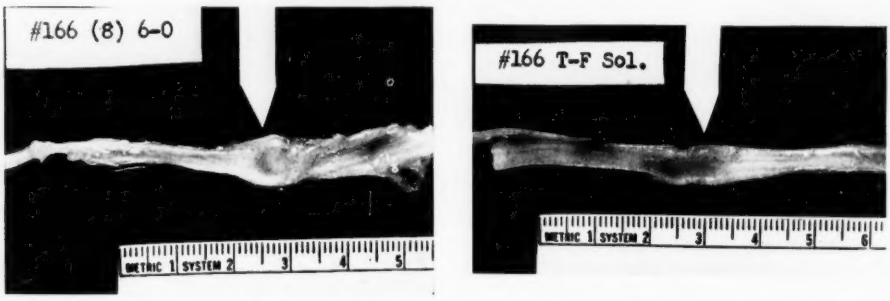

Fig. 2*B*.—Photographs of dog sciatic nerves removed at autopsy 12 weeks after operation.

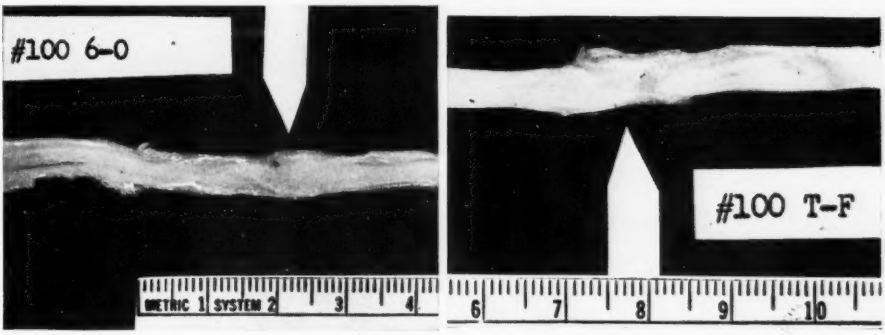

Fig. 2*C*.—Photographs of dog sciatic nerves removed at 26 weeks.

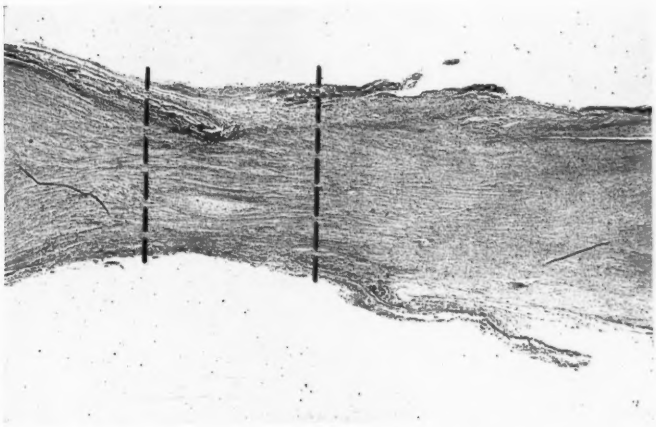

Fig. 3*A*.—Photomicrograph of dog sciatic nerve with thrombin-fibrinogen coagulum anastomosis four weeks old. Longitudinal section through anastomosis, 72 Micro Tessar.

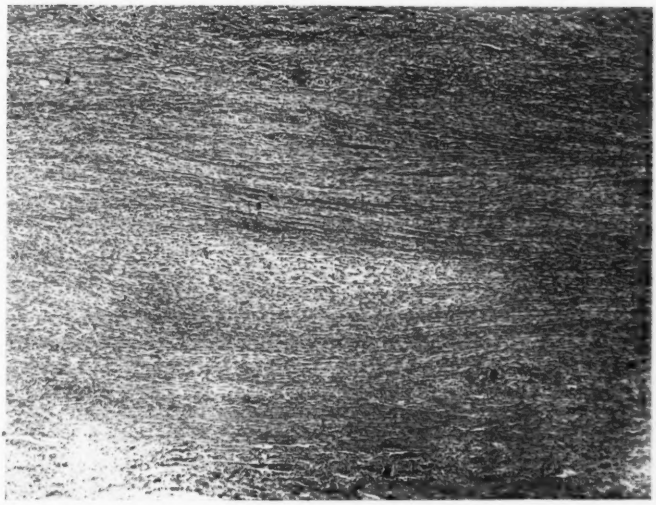

Fig. 3*B*.—Same as Figure 3*A*. Area of anastomosis (within dotted lines). Coagulum absorbed; inflammatory reaction absent. Active proliferation of nerve sheath cells and fibroblasts. Hematoxylin and eosin; reduced from mag. × 80.

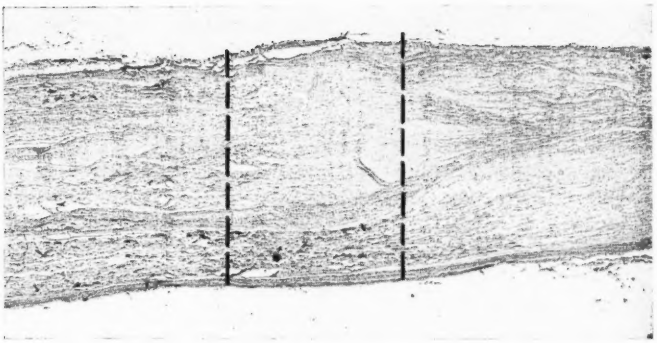

Fig. 4*A*.—Photomicrograph of dog sciatic nerve with thrombin-fibrinogen coagulum anastomosis 18 weeks old. Longitudinal section through anastomosis, 72 Micro Tessar.

Fig. 4*B*.—Same as Figure 4*A*. Area of anastomosis (within dotted lines). Distinct nerve fibers with myelinated sheaths crossing anastomosis within epineurium. Hematoxylin and eosin; reduced from mag. × 70.

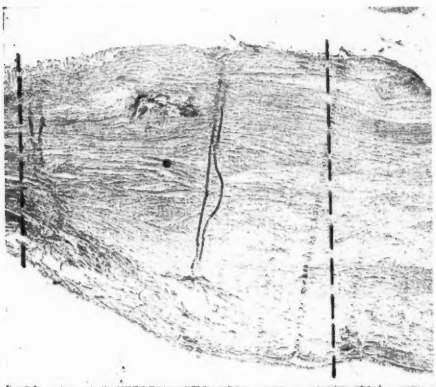

Fig. 5*A*.—Photomicrograph of dog sciatic nerve with silk suture anastomosis 20 weeks old. Longitudinal section through anastomosis, 72 Micro Tessar.

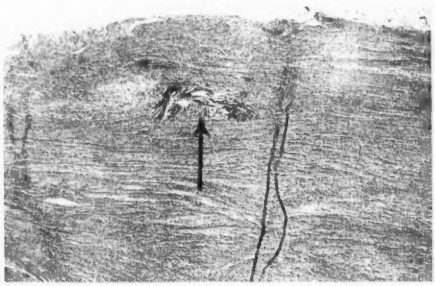

Fig. 5*B*.—Same as Figure 5*A*. Area of anastomosis (within dotted lines). Anastomosis more bulbous, with granuloma present around silk suture (arrow). Hematoxylin and eosin; reduced from mag. × 70.

Schwann cells with fibroblasts were seen infiltrating the coagulum and bridging the anastomosis. By two weeks the chronic reaction had been largely replaced by a stage of proliferation of fibroblasts and neurilemmal sheath cells. The anastomosis looked firm, with intact epineurium and perineurium. All evidence of inflammatory reaction had subsided by the third week. Thereafter, proliferation and alignment of neurilemmal sheath cells with maturation of the fibroblasts continued. By 16 weeks distinct nerve cylinders with myelinated sheaths were seen crossing the anastomosis within the epineurium and entering the distal nerve segment. At 22 weeks mature bundles of myelinated nerve fibers, now well organized, were seen progressing down the distal nerve trunk. By 28 weeks the anastomosis was completely bridged by normal-appearing myelinated nerve fibers which

could be seen in the most distal sciatic nerve cross section.

In the silk-suture anastomoses without coagulum, the healing progressed with a similar pattern. After the third week, when the coagulum was largely absorbed and replaced by proliferating nerve elements, the appearances of suture and coagulum anastomoses were essentially the same. There was one significant difference, however: a chronic inflammatory foreign-body reaction with localized granuloma formation persisted about the silk sutures.

The nerve function studies demonstrated that the apparent rate of regeneration was the same with both the coagulum and the silk anastomoses. Both electromyography and electrodiagnostic testing showed no apparent evidence of peripheral nerve regeneration until the second month. This progressed, and by six to seven months nerve regeneration was practically complete, as shown by an occasional fasciculation voltage complex and numerous motor units on the electromyogram and by a return to a normal chronaxie and strength duration curve on electrodiagnostic testing. With one unexplained exception, the nerve regeneration tests correlated well with the gross and microscopic findings.

Comment

The method of nonsuture anastomosis between the severed ends of dog sciatic nerve was simple and effective. The coagulum held the ends together even under moderate tension. When the coagulum anastomosis was not entirely satisfactory, it could be reinforced with additional thrombin and fibrinogen or quickly wiped away and a new one formed. If a coagulum of greater tensile strength desired, the amount of powdered fibrinogen and/or the concentration of the thrombin solution could be increased.

There was no evidence of delayed lysis of the coagulum, nor did any nerve ends separate postoperatively. The coagulum did not interfere with nerve regeneration, as shown by nerve regeneration tests and histologic examination. There appeared to be no increased fibrosis with the coagulum anastomosis, as compared with the silk. Foreign-body reaction with localized granuloma formation persisted around the silk sutures. Although heterologous, the purified bovine thrombin and human fibrinogen were well tolerated in the dog.

It would be advantageous to have the lyophilized fibrinogen prepared and marketed in smaller vials, containing less fibrinogen. This, in turn, would decrease the number of times that a vial would be reused before the contents were exhausted. This is of considerable practical importance, because our studies have shown a marked decrease in tensile strength of a coagulum made from fibrinogen that has been left out of refrigeration for even a short period. Finally, if this method is to be used in the human, it should be noted that the method of sterilization of this fibrinogen preparation by ultraviolet radiation might not completely inactivate the virus of homologous serum jaundice, if this were present in the original plasma.

In this study it was not necessary to add tension sutures to the coagulum anastomosis to prevent nerve-end separation. Under conditions of greater tension, especially in the vicinity of joints, the addition of several tension sutures may be necessary. Even here the coagulum may be of benefit by decreasing the number of sutures required. The coagulum may also act as a protective cuff against adjacent fibrous infiltration.

This method appears to be particularly desirable for smaller nerves. Here, the ratio of sutures to nerve is greater and the accurate alignment under proper tension without injury of nerve fibers may be more difficult with suture than with coagulum. Our attention was particularly drawn to this problem concerning the phrenic nerve which has been observed to be injured at surgery or locally involved in recent inflammatory fibrosis or neoplasm. In a case of excision of the involved nerve segment, either with direct end-to-end anastomosis

or possibly with the aid of an interposed nerve graft, the coagulum could be of help in reestablishing diaphragmatic action and augmenting depressed respiratory function. Obviously, the method of nonsuture coagulum anastomosis should be applicable to many other small nerves and peripheral nerves.

Because the coagulum does not interfere with the distal growth of nerve fibers, it may be of use as a prosthetic bridge across widely gaping nerve ends. We have been able to make hollow, flexible, tubular molds of any length and diameter by repeatedly dipping rods into a solution of liquid latex. After drying, the rod is removed, leaving a cylindrical jacket of rubbery latex which can be slit longitudinally, sterilized, and placed between the widely separated nerve ends. The thrombin-fibrinogen coagulum can be formed in the latex mold and the mold then removed. The resulting coagulum bridge maintains its shape and effectively adheres to both nerve ends. The use of the coagulum for this purpose is being investigated further.

Summary

A simple method of making an effective coagulum from topical thrombin and purified fibrinogen for nonsuture nerve anastomoses is described.

The coagulum effectively held severed sciatic nerves of dogs in apposition without untoward reaction.

On the basis of careful gross and histological examinations and comparative electromyography and electrodiagnostic testing of nerve regeneration, the coagulum anastomoses were as effective in this test series as control silk-suture anastomoses.

Possible applications of the method are briefly discussed.

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Experimental Reconstruction of Ureters

Substitution with Autogenous Pedicled Fallopian Tube Grafts

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Introduction

The clinical and experimental repair of long ureteral defects remains a challenging problem. An ideal ureteral substitute should simulate the form and function of the normal ureter. The use of Fallopian tube as a conduit to replace ureter is suggested by the following features:

(1) The anatomic proximity of the two organs.
(2) The expendability of Fallopian tube.
(3) The fact that both possess a mucosal lining and a muscular wall with peristaltic activity.
(4) The manipulable blood supply of the tube, which need not be compromised when used as a pedicle graft to replace a segment of ureter.
(5) The avoidance of problems of antigenicity and foreign-body reaction when an autogenous graft, rather than a homologous structure or an inorganic tube, is substituted for ureter.

This report is concerned with the experimental reconstruction of long ureteral defects by the use of substitute Fallopian tube pedicle grafts.

Method

Nineteen female mongrel dogs, ranging in weight from 19 to 52 lb., were used, without special preoperative preparation. A standard veterinarian solution of pentobarbital (Nembutal) was administered intravenously for anesthesia. The peritoneal cavity was entered through a left rectus, muscle-splitting incision, and the left uterine horn was mobilized. The uterotubal junction was incised between a crushing and bulldog clamp, the latter being applied to the tube because it permitted atraumatic manipulation of the end to be used for anastomosis. The mesosalpinx was divided in the avascular zone so as to preserve the arcuate blood supply of the tube. The crushed uterine end was suture-ligated and invaginated into the body of the uterus, and the raw surface was peritonealized.

The ovarian end of the tube was divided, with a bulldog clamp applied at the end to be anastomosed. The pedicled tubal graft was now mobile with its blood supply undisturbed, as evidenced by active bleeding at its ends upon removal of the bulldog clamps. The tubal grafts varied from 3 to 10 cm. in length and from 0.4 to 1.6 cm. in width, depending upon the weight of the animal and the phase of estrus activity.

The distal two-thirds of the ureter was mobilized intraperitoneally, with attention to preserving the periadventitial blood supply. A segment of ureter corresponding to the length of the pedicled tubal substitute was resected. The excised ureteral segments varied from 3 to 10 cm. in length and from

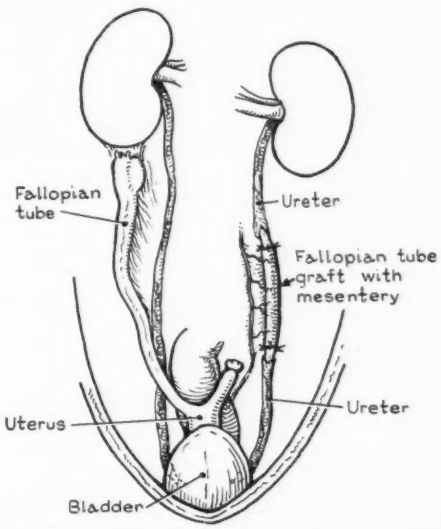

Fig. 1.—The operative technique (ureterotubo-ureterostomy) is diagrammatically illustrated.

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From the Surgical Research Laboratory and the Urological and General Surgical Services, Montefiore Hospital.

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0.15 to 0.3 cm. in diameter. Two reconstructive procedures were employed. One consisted of a ureterotuboureteral anastomosis; the other, of a ureterotubovesical anastomosis. In the former, end-to-end anastomoses were performed with use of over-and-over or interrupted sutures* at four cardinal points, incorporating all layers of both graft and ureter. Where a leak was detected, an additional interrupted suture was taken for reinforcement.

The second type of reconstruction (Fig. 1) was performed in order to eliminate the need for a distal tuboureteral anastomosis and to avoid the normal disparity in the diameters of tube and ureter. The latter was accomplished by suture-ligating the distal end of the tubal graft and performing a Cordonnier end-to-side ureterotubostomy. This method permitted the approximation of equal diametric orifices and accurate mucosal coaptation. The former was achieved by a direct fish-mouth implanatation of the uterine end of the tubal graft into the posterior wall of the bladder, above the normal ureterovesical junction.

The contralateral genitourinary tract was not disturbed, in order to permit serially controlled urographic and postmortem comparisons between the normal and operated sides of the same animal. The abdomen was closed in layers. The anastomotic area was drained through a stab wound in the flank. Each dog received 1000 cc. of 5% dextrose in water intravenously during the operation and 300,000 units of penicillin and 0.5 gm. of streptomycin daily for one week postoperatively. The drain was removed on the fifth postoperative day.

In two dogs the right rather than the left genitourinary tract was used. Three animals in whom ureterotuboureteral anastomosis was performed were subjected to complimentary nephrostomy so as to observe the effect of urinary diversion. Cabot's technique was employed to insert the nephrostomy tube, as splitting the kidney was considered too traumatic.

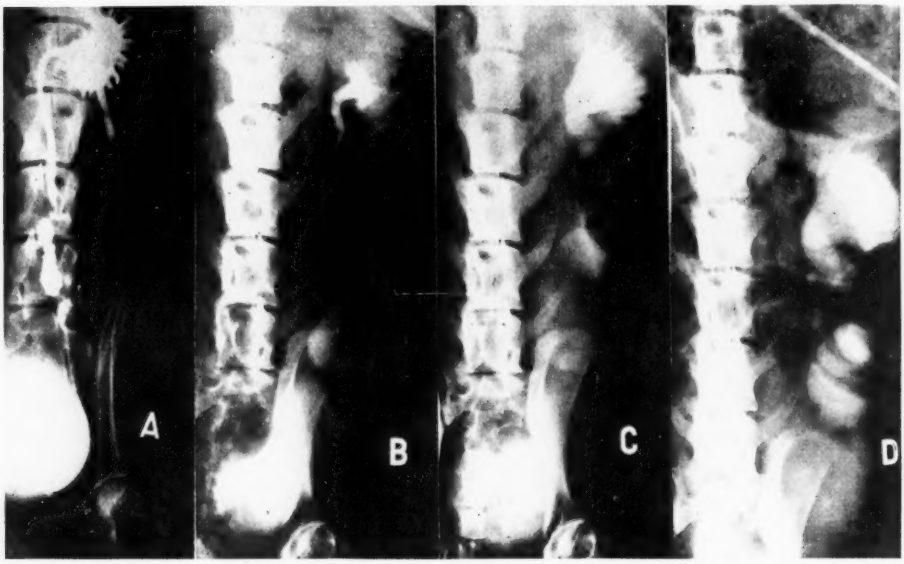

Fig. 2.—*A*, antegrade insertion of dye via nephrostomy tube, 21 days after ureterotuboureterostomy. *B*, excretory urogram, 35 days after operation. Pooling of dye within the slightly dilated graft is present. *C*, excretory urogram, 70 days after operation. Dye has collected within the dilated graft, and proximal hydronephrosis is evident. *D*, excretory urogram, 120 days after operation. Note the markedly dilated, redundant graft, with advanced hydroureter and hydronephrosis.

Results

A total of 19 dogs were utilized for these observations. One died of a convulsive seizure during intravenous urography on the 14th postoperative day. Three animals succumbed to bronchopneumonia. Six died of generalized peritonitis, secondary to urinary extravasation from

* No. 00000 medium chromic absorbable surgical (gut) suture, armed with an Atraumatic curved noncutting needle at each end, supplied by Ethicon Suture Laboratories, New Brunswick, N. J.

technical anastomotic errors. It is important to note that all anastomotic leaks were fatal. There was no walling-off process within the peritoneal cavity and no possibility of creating an independently drainable pocket as in ureteral reconstructive procedures previously reported.† Where the anastomotic leak was small the animal survived with the formation of a perianastomotic abscess. This led to fibrosis and stricture at the suture line, with resultant obstructive uropathy and progressive loss of renal function.

Nine dogs survived for sufficient periods to study the fate of the grafts and the urologic sequelae. Four of these had been subjected to ureterotuboureterostomy; the remaining five, to ureterotubocystostomy. The animals were killed at intervals ranging from 15 to 120 days after operation. No appreciable differences could be demonstrated between the two types of procedures in graft behavior or long-term results.

Radiographic Findings.—Serial intravenous urograms, or antegrade studies by dye insertion through the nephrostomy tubes, were performed at 10- to 14-day intervals after operation. Prior to the 21st postoperative day no functional or anatomical alterations could be demonstrated in the graft, kidney, or ureteral segment of the side (Fig. 2*A*). Dilatation of the tubal graft became evident thereafter (Fig. 2*B*). The degree of dilatation increased with the prolonged survival of the experimental animal, so that the dye-filled graft appeared as a curled, redundant, sausage-like sac (Fig. 2*C*). Changes in the graft were accompanied by proximal hydroureter and hydronephrosis. By the 120th postoperative day dye excretion was delayed and a severe obstructive uropathy was present (Fig. 2*D*).

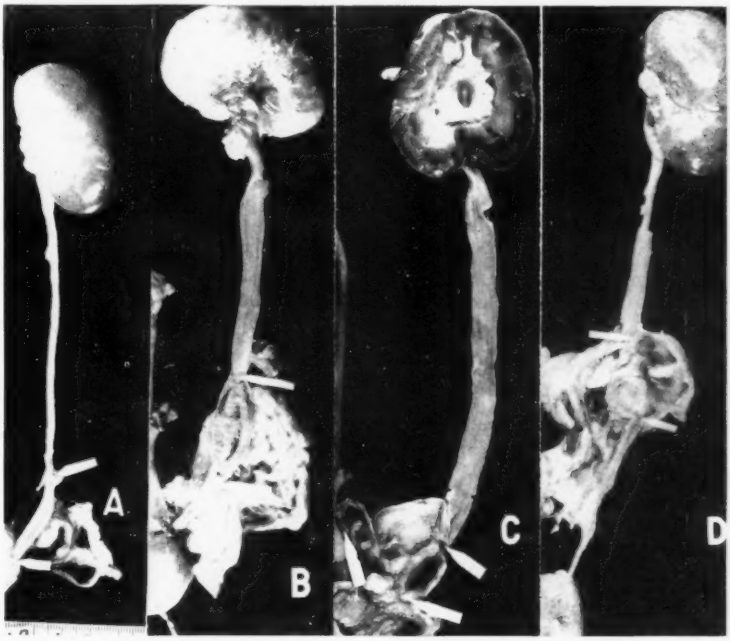

Fig. 3.—*A*, gross specimen, 22 days after ureterotubocystostomy. The graft is delineated between the arrows, with vascular pedicle still intact. It appears as normal tube. *B*, gross specimen, 37 days after ureterotuboureterostomy. Note early proximal hydroureter. *C*, gross specimen, 123 days after ureterotuboureterostomy. The graft is a thick-walled redundant sac.

Necropsy and Histological Findings.—At autopsy the gross changes in the graft paralleled the radiographic findings. In the

† References 1 and 2.

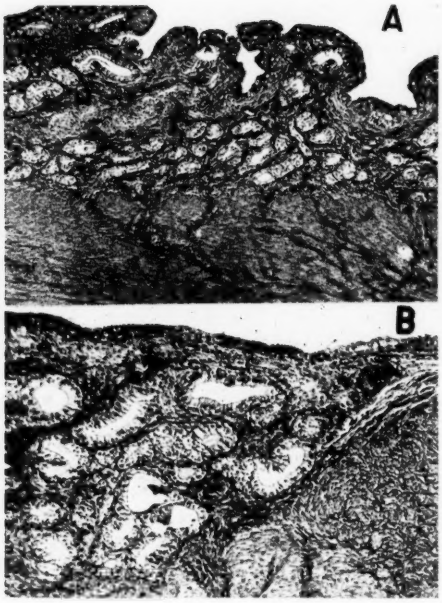

Fig. 4.—*A*, photomicrograph of tubal graft, 22 days after ureterotubocystostomy. Note the normal papillary tufting of the mucosa. Hematoxylin and eosin; reduced from mag. × 100. *B*, photomicrograph of tubal graft near proximal anastomosis, 37 days after ureterotuboureterostomy. Papillary tufting has disappeared. Hematoxylin and eosin; reduced from mag. × 150.

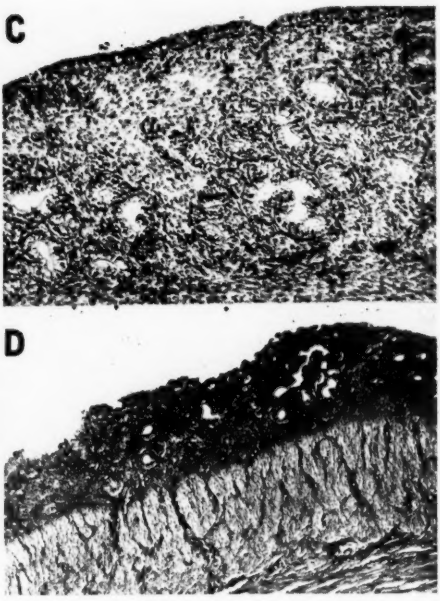

Fig. 4.—*C*, photomicrograph of tubal graft, 75 days after ureterotubocystostomy. The stroma appears edematous, and surface epithelium is smooth. Glands are still actively secreting mucus. Hematoxylin and eosin; reduced from mag. × 130. *D*, photomicrograph of tubal graft, 123 days after ureterotuboureterostomy. The mucosa is slightly hypoplastic but still recognizable as tubal. The inner muscle layer shows hypertrophy. Masson's trichrome stain; reduced from mag. × 50.

first three weeks after operation no anatomical changes were noted in the graft (Fig. 3*A*). Histologically it appeared as essentially normal tube (Fig. 4*A*). At 35 days dilatation of the lumen was seen and the mucosal lining was somewhat flattened (Fig. 3*B*). Microscopic sections showed this to be associated with a loss of papillary tufting, but the mucosa retained its characteristic lining of columnar epithelium and there was no loss of actively secreting glands (Fig. 4*B*). At 70 days dilatation of the graft and proximal hydroureter and hydronephrosis were more pronounced. The walls of the graft appeared much thicker, and the mucosal surface was entirely smooth (Fig. 3*C*). On histological study, there was a total loss of papillary tufting, though the mucosa was still lined by columnar cells. The stroma appeared edematous, and glands were less closely packed, though still actively secreting mucus (Fig. 4*C*). Both muscle layers were hypertrophied, with no fibrous tissue replacement. At 120 days the tubal graft had become a markedly dilated, fusiform sac, convoluted upon itself. The mucosa was thin and smooth, but the muscle wall was even more thickened (Fig. 3*D*). Histologically the mucosa was hypoplastic but still recognizable as tubal in origin (Fig. 4*D*). Although some of the columnar cells lining the surface had sloughed, there was no substitution by ingrowth of transitional cell epithelium from the adjacent ureter and bladder. Glands were decreased in number, and the surrounding stroma showed slight inflammatory-cell infiltration and minimal interstitial fibrosis. Acinar cells appeared more cuboidal than columnar, and secretion was scant. Hypertrophy of the circular and longitudinal muscle layers was pronounced.

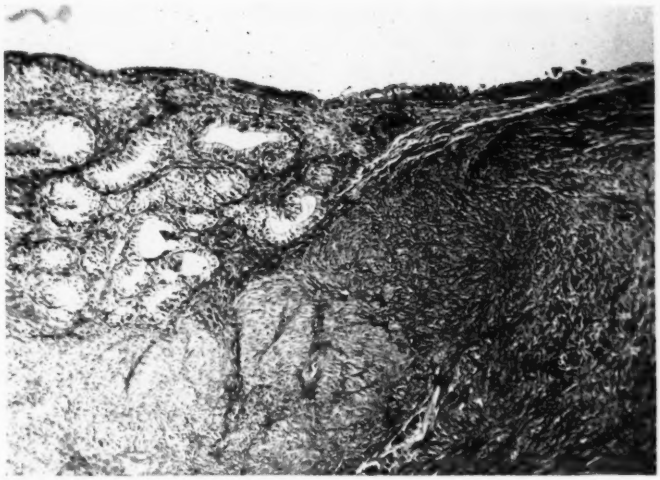

Fig. 5.—Photomicrograph of proximal anastomosis, 37 days after ureterotuboureterostomy. Note the abrupt transition from the transitional-cell epithelium of the ureter on the right to the glandular mucosa of the Fallopian tube graft. Hematoxylin and eosin; reduced from mag. × 150.

Anastomoses.—At the site of ureterotubal anastomosis, healing occurred by fibrous union, with each organ maintaining its own mucosal and architectural pattern (Fig. 5). In no case did uroepithelium proliferate beyond the anastomosis. The fibrous union resulted in severe stricture in one case, mild stricture in three, and minimal to no stricture in the remaining five. However, unrelated to the degree of anastomotic cicatrization, all cases exhibited progressive obstructive uropathy as evidenced by hydroureter and hydronephrosis proximal to the site of graft insertion. In no case was the kidney normal at time of post-mortem examination.

At the site of tubovesical anastomosis only one case of mild stricturization was encountered, and in this a small calculus was found just above the site of tubal implantation into the bladder.

Diversion of Urinary Stream.—In three cases preliminary nephrostomy was undertaken to evaluate the effects of defunctionalization on the fate of the graft on anastomotic healing. No appreciable alteration on either of these could be demonstrated by this measure. The progressive changes in the graft, anastomoses, and proximal urinary tract were the same, with or without nephrostomy.

Comment

The problem of replacing long segments of traumatized or diseased ureter has challenged the urologist since the turn of the century. The utilization of foreign bodies such as rubber, glass, or silver tubes as substitute ureters eventuated in anastomotic disruption and fibrosis, tube migration, and urinary extravasation.[3] Insert tubes of tantalum, Vitallium, and polyethylene have also failed to reestablish urinary tract continuity.‡ The use of homologous ureteral grafts has been attended by antigenic tissue reaction and graft necrosis.[6] Lyophilized arterial and ureteral grafts have undergone gradual absorption and replacement fibrosis.[8] Pedicled abdominal wall grafts have developed ossification within the fascial layer, and free grafts of fascia, peritoneum, and bladder have sloughed or fibrosed when used to replace ureter.§ Fresh autogenous venous and arterial grafts have failed to survive because of inadequate blood supply.‖

‡ References 4-6.
§ References 2 and 5.
‖ References 3 and 6-9.

and attempts to vascularize such grafts by burying them in submucosal intestinal tunnels have resulted in prolonged survival but ultimate degeneration of the grafts.¶

The greatest potential for successfully replacing a long segment of ureter could be anticipated by the substitution of an autogenous expendable tubal structure lying in close proximity to the ureter and with an intrinsic blood supply. Thus, in the preantibiotic area, intestinal loops, appendix, bladder flaps, and Fallopian tubes were employed for this purpose,[3] but these experiments were accompanied by a formidable postoperative mortality from infection and peritonitis, so that long term follow-up studies could not be made.

In recent years, the successful use of pedicled bladder flaps has been reported by numerous investigators,# but the procedure is long, arduous, and painstaking. It has been complicated by anastomotic cicatrization and reflux, and it is limited to replacing the distal ureter.

The revival of the utilization of ileal loops to replace ureteral segments has met with considerable success in the hands of McLean and Fais, Rack, Davids and Lesnick, and Foret and Heusghem.* A comparison of their results with ours is of considerable interest, in that it may account for the progressive obstructive uropathy which we encountered when employing pedicled Fallopian tube grafts.

With both ileal loops and Fallopian tubes, the grafts remained viable and the normal mucosal architecture was maintained. Davids and Lesnick [19] described minimal mucosal hypoplasia of the ideal loop, and McLean and Fais [17] cited slight uroepithelial overgrowth at the anastomotic sites, but the epithelium remained intestinal in their work, as it remained tubal in this study. The fate of the mucosa in substitute ureteral grafts is the subject of a separate communication.[22]

The major difference, then, is the luminal dilatation and muscular wall hypertrophy which we noted, eventuating in proximal hydroureter and hydronephrosis, whereas the intestinal loops which others employed maintained their normal caliber and muscular structure. This difference in graft behavior can be explained in terms of the normal function of the viscera.

The ileum is a distensible tubal structure, one of whose basic functions is the continuous peristaltic propulsion of large amounts of fluid and semisolid material through the alimentary canal. Thus, its conversion to a vehicle for the transport of large quantities of urine, rather than intestinal content, places no extra load upon it, for this is a function for which it requires no special adaptation. On the other hand, the Fallopian tube is biologically constituted to respond to hormonal stimulation only periodically, transporting ova in a small mucoid medium toward the uterus. When it is suddenly called upon to carry a much larger amount of fluid, a function which it has never had and for which it is neither anatomically nor physiologically intended, it is unable to adapt to this demand. Though capable of peristalsis, the contractile power of the muscle layers is insufficient to propel such large quantities of fluid toward the bladder. As the volume of urine increases, intraluminal pressure rises and the tube dilates. In the attempt to evacuate the increased luminal content, the muscle wall undergoes hypertrophy and hyperplasia. However, it is inadequate to the task and eventually the tubal graft becomes a decompensated sac filled with static urine. Backflow pressure results in proximal hydroureter and hydronephrosis. The tube of the dog represents part of a bicornuate uterus and differs from the human oviduct in relative luminal area, degree of muscular development, and the mobility of its attachments. Therefore, the conclusions drawn are pertinent only for the dog.

¶ References 1 and 2.
# References 10-16.
* References 17-21.

Summary

Pedicled Fallopian tube grafts were used to bridge ureteral defects in dogs.

Dilatation of the graft lumen and muscular wall hypertrophy and hyperplasia eventuated in proximal hydroureter and hydronephrosis.

The Fallopian tube is not biologically constituted to function as a substitute ureter in the transport of urine from kidney to bladder, in the dog, when the experimental methods detailed above are used.

Dr. Lazarus A. Orkin gave help and suggestions, and Mr. Ruthven Ferreira and Mr. Ivan Alfonso Henry gave technical assistance.

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Central Respiratary Depression Produced by Myoneural Blocking Agents

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The occurrence of prolonged apneas following the anesthetic use of myoneural blocking agents has been of sufficient magnitude to warrant a substantial number of case reports in the literature.* Suggestion of central respiratory depression by these drugs has been made in clinical observations[3] and in laboratory investigation,† in spite of the now classic report of Scott Smith[6] discounting the possibility of central effects of curare, and in spite of the theoretical postulate proposed by Riker,[7] that quaternary compounds with "onium" charges are of such a critical molecular size that they cannot penetrate the cell barriers of the central nervous system.

Over a period of 36 months, we observed in a series of approximately 3800 patients who received some form of myoneural blocking agent 13 patients whose clinical picture strongly suggested the presence of central respiratory depression. An attempt has been made to carefully evaluate these cases to determine if there was some common denominator other than the use of muscle relaxants in the production of this clinical syndrome. A clinical evaluation of the therapeutic measures employed in reversing this central depression has also been attempted.

The clinical picture which developed in the 13 patients, the data on whom will be subsequently presented, can perhaps be best depicted by reporting a typical protocol.

Recorded for publication Oct. 3, 1955.

From the Department of Anesthesiology of the Albany Medical College of Union University and the Albany Hospital.

* References 1 and 2.

† References 4 and 5.

Report of a Case

The patient was a 72-year-old woman who came to the operating room in August, 1953, for a proposed partial colectomy and ileosigmoidostomy. In February, 1953, she had had a colostomy for a carcinoma of the transverse colon, which had been resected at that time, without anesthetic incident. In May, 1953, the colostomy had been closed, again without anesthetic incident. Subsequently it became evident that she required a re-resection of her colon and an ileosigmoidostomy, and she was brought to the operating room for this procedure in essentially good condition for a woman of her age. Her blood pressure was 130/70; her lungs were essentially clear except for a few scattered rales at the right base, and her genitourinary system, neurological system, and metabolic survey were considered within normal limits. She had a recorded hemoglobin of 11 gm. prior to one preoperative transfusion, with an associated hematocrit of 40% and white blood cell count of 5900. Her blood chemistry values were reported as essentially normal. As had been done with her two previous anesthetic procedures, anesthesia was induced with 300 mg. of 5% thiopental (Pentothal) sodium and orotracheal intubation accomplished after relaxation had been produced with 3 mg. of decamethonium bromide (Syncurine). Her subsequent anesthetic management was with cyclopropane and oxygen, with intermittent small doses of *d*-tubocurarine chloride to provide adequate relaxation, the total dosage of *d*-tubocurarine chloride over a period of two hours being 10 mg. After peritoneal closure, anesthesia was maintained with nitrous oxide-oxygen in a semiclosed system, this for a period of approximately 20 minutes. Throughout the entire procedure ventilation was controlled, and the remainder of the patient's vital signs remained stable. As the skin was being closed, it became apparent that the patient was not about to resume her own ventilation. In an attempt to stimulate spontaneous ventilation, the nitrous oxide was turned off, the system closed, and with 100% oxygen running the CO_2 canister was turned off and the patient made to rebreathe her own carbon dioxide. After a period of eight minutes of re-

breathing, the patient still did not attempt to ventilate on her own. A suction catheter was introduced through the endotracheal tube, and when the carina was stimulated the patient coughed several times, but in the absence of carinal stimulation she persisted in her apnea. Edrophonium (Tensilon) chloride, 10 mg. in 5 mg. divided doses spaced four minutes apart, was given to the patient without any apparent results. Since this patient had not received any supplemental meperidine (Demerol) hydrochloride beyond the 75 mg. given three hours before this period as preoperative medication, it was decided not to attempt the use of the narcotic antagonist, nalorphine (Nalline) hydrochloride, which procedure would have been followed had the patient received any supplementary narcotic during the operative procedure. Because of our previous experience with nikethamide (Coramine) in situations similar to this, it was given rapidly intravenously in dosage of 1125 mg. Within a period of less than 45 seconds, the patient began to breathe vigorously, opened her eyes, and removed her own endotracheal tube. Subsequent ventilatory exchange as watched carefully in the recovery room remained quite adequate with no evidence of impaired function. Her postoperative course was totally uneventful, and she was discharged home 19 days after her surgery.

This, briefly, is the pattern assumed by the other patients herein reported, namely, that of inadequate or absent ventilation at the end of surgery following the use of curare-like drugs. These apneas did not respond to the usual methods of therapy but responded immediately to the stimulus of fairly large doses of intravenous nikethamide. Summary of the data of the other cases that fit the pattern of "central respiratory depression" is listed in the attached tables (Tables 1 and 2).

TABLE 1.—*Summary of Anesthetic Agents and Techniques*

	Patients, No.
A. Premedication (appropriate for each patient)	
Barbiturate, morphine, atropine	3
Barbiturate, meperidine, atropine	4
Morphine, atropine	1
Meperidine, atropine	2
Chloral hydrate, meperidine, atropine	2
No premedication	1
B. Agents	
Thiopental-N_2O	3
Thiopental→cyclopropane	4
Thiopental→cyclopropane→N_2O	5
Thiopental→ether→N_2O	1
C. Primary method	
Semiclosed circle absorption	4
Closed circle absorption→semiclosed	5
Closed circle absorption	4
D. Primary technique	
Controlled ventilation	11
Assisted ventilation	2
E. Relaxants	
Succinylcholine chloride + *d*-tubocurarine	7
Decamethonium bromide + *d*-tubocurarine	4
Succinylcholine chloride (I. V. drip)	1
Decamethonium bromide	1

Comment

Careful search of the data on the patients reported above was not particularly enlightening. The cases as reported were all anesthetized by residents in training or nurses. Although a greater number of them fell in an age group of more than 50 years, this was not considered significant, since there were several patients in a much younger age group. Ten patients had elective surgery performed. Three were operated upon as emergencies. The duration of illness leading to surgery ranged from nine hours to seven years. Although the majority of the cases reported had gastrointestinal pathology, particularly of the upper gastrointestinal system, this was not an absolute finding in all the cases. Only one case had recognizable respiratory disease. The preoperative laboratory data, although it was incomplete in many cases, was essentially within normal limits, except for abnormal liver function tests in five patients. There

TABLE 2.—*Dosage Schedule of Relaxants**

Drug		Mean Dosage, Mg.		Range, Mg.	
A	B	A	B	A	B
Succinylcholine +	*d*-Tubocurarine	40	18	30-310	3-33
Decamethonium +	*d*-Tubocurarine	3.6	16	3-4	10-27
Succinylcholine +	None	300	0	300	0
Decamethonium +	None	1.5	0	1.5	0

* Average Duration of Cases—171 min. (Range 40″ to 7′ 25″)

were insufficient postoperative laboratory data upon which to draw any conclusions. There was no mortality in this series of patients, nor was their convalescence unusual in any way. The premedication for these patients was varied, and no one premedicant drug was a common denominator to all. Likewise, no one anesthetic agent could be implicated, since there was a considerable variety employed; although thiopental sodium was used in all these cases, in most it was used merely for induction and all patients breathed spontaneously after intubation until controlled or assisted ventilation intervened. We did not consider the dosages of the relaxant drugs used to be abnormally high, and again it is to be noted that when relaxants were used in combination the patient was allowed to ventilate spontaneously after the first relaxant before introduction of a second relaxant. Both semiclosed and closed systems of anesthesia were employed, singly and in combination. Although the ratio of controlled ventilation to assisted ventilation is 5½ to 1 in the 13 cases reported, this factor is not as significant as it appears, since in all cases in which ventilation is augmented in our institution the ratio of controlled to assisted ventilation is approximately 4½ to 1.

Thus, from our observations and critical evaluation of patient status and anesthetic management there appeared to be no single factor that would give us some previous warning that inadequate ventilation, resistant to usual forms of therapy, would occur.

The failure of edrophonium chloride to reverse "curare apnea" lends itself to some conjecture. Curare antagonism by edrophonium chloride is dramatically demonstrated in the animal nerve-muscle preparation when administered at the point of beginning recovery. Reversal with edrophonium chloride can also be demonstrated in the cat's sciatic nerve-gastrocnemius muscle preparation during complete paralysis within relatively narrow limits. It is thus possible in the cat to paralyze with *d*-tubocurarine and reverse with edrophonium chloride and repeat this several times in the same preparation. Hoppe ‡ reports that while edrophonium chloride effectively antagonizes *d*-tubocurarine repeatedly in the cat's sciatic-gastrocnemius preparation, he is not so certain that it is equally effective in antagonizing the effects on respiration. In the sciatic-gastrocnemius muscle preparation, the influence of the central nervous system is cut off and the effects of edrophonium chloride are measured at the neuromuscular junction. It is not possible to extrapolate the effects of edrophonium chloride at the neuromuscular junction of the gastrocnemius to the respiratory musculature in this preparation, since the influence of the intact central nervous system on the latter muscle system has not been eliminated. Edrophonium chloride may restore the ability to transmit impulses at the neuromuscular junction in the respiratory musculature, but this would not be particularly helpful if there were no impulses forthcoming from the central nervous system. Hoppe believes that edrophonium chloride is an anticurare agent which facilitates recovery of neuromuscular transmission *after* it is evident that there is some transmission occurring at the neuromuscular junction, in contrast to restoring transmission in the presence of total paralysis; and this applies to the respiratory muscles even more vigorously than to the peripheral muscles. He estimates that if there are no visible signs of respiratory efforts after the administration of a total of 15 mg. of edrophonium chloride, further doses should not be given because of the risk of imposing additional neuromuscular block with the edrophonium itself. He states categorically that there still is no thoroughly dependable pharmacological antagonist for curare apnea.

The failure of nalorphine hydrochloride to reverse the inadequate ventilation seen in those cases in which narcotics in addition to that used for premedication were used is not surprising. To utilize this drug

‡ Hoppe, J. O., personal communication to the authors.

in the absence of true narcotic depression is certainly unwise, since there is sufficient evidence available to show that the addition of nalorphine hydrochloride to non-narcotized and depressed persons will merely produce additive depression.§ Its use in dosage of 10 mg. or less as a therapeutic test in those cases in which narcotics have been used freely is certainly warranted, but we feel that the injudicious use of more than 5 to 10 mg. of nalorphine hydrochloride or other similar narcotic antagonists may further jeopardize the patient suffering from inadequate or absent ventilation due to causes other than narcotic depression.

That some abnormal sensitivity or threshold exists in the respiratory center of the patients reported herein is apparent when one considers the failure of the center to respond to the challenge of extremely high CO_2 concentrations in the lung air. It is abundantly evident that CO_2 stimulus-response observations represent the most adequate method of testing respiratory center activity,[10] and the failure of these patients to respond at all to such a stimulus after peripheral block has been demonstrated to be absent by producing muscular contraction with carinal stimulation leads automatically to the supposition that the respiratory center is in an abnormal state of sensitivity. This is particularly more evident when one considers the almost phenomenal and immediate response to the injection of nikethamide into these patients, which injection apparently very rapidly alters the status of the respiratory center.

Although we have observed in at least one postanesthetic neurosurgical patient suffering an apnea of undetermined etiology a "hypoventilation syndrome" type of response to a verbal command, none of the 13 patients reported here responded to the stimulus of vocal command.

The remarkable response to the intravenous injection of rather large doses of nikethamide leaves little doubt in our minds as to the cause and effect relationship between the drug and the response. However, the physiological mechanism involved remains completely unsolved in our minds. It is assumed from the rather scant data in the literature[11] that nikethamide produces a respiratory-center response by way of carotid-area mechanisms, and perhaps in our cases this is the only type of stimulus to which the respiratory center will respond. The chemical structure of nikethamide is in no way similar to that of curare in the type of relationship that exists between nalorphine and morphine, levallorphan and methorphinan (Dromoran), etc., and it is quite logical to assume that the mechanisms of reversal of "central apnea" cannot be likened to the antagonism of nalorphine to morphine by substitution of a weak narcotic effect for a potent one. It has been stated that α-lobeline is likewise effective in clinical syndromes such as we have described,[3] but in one case in which we have used the drug it was as completely ineffective as all other methods of therapy employed.

Thus, insofar as we have been able to determine, there is no valid explanation, other than central depression, for the occurrence of this clinical syndrome, no prognostic sign as to its possible occurrence, and no valid explanation for the effectiveness of nikethamide therapy. True assessment of even the existence of central depression from curare-like drugs appeared to lie only in carefully prepared and carefully controlled cross circulation experiments in animals. By completely severing all vascular connections between the head and body of a recipient dog and supplying circulation to the avascular cerebrum from a donor dog, the introduction of muscle relaxants into the donor dog has proved the existence of pure central depression in the recipient dog.‖ On the basis of the postulate that if true central depression is produced by muscle relaxants the recipient dog will develop inadequate or absent ventilation, Hoppe has demonstrated the validity of the clinical syndrome previously described.

§ References 8 and 9.

‖ Hoppe, J. O., unpublished data.

Further assessment of the nature of this "central" effect may elucidate the mode of action of nikethamide in reversing it.

Summary

A critical evaluation of 13 cases in which clinical "central respiratory depression" occurred after the use of myoneural blocking agents is presented. A discussion of the attempted therapeutic measures is given.

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The Cerebral Physiology of Controlled Hypotension

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Controlled hypotension is not infrequently induced to diminish operative bleeding, and in neurosurgical procedures, for the additional purpose of decreasing brain tension. There is considerable question as to whether the advantages of the procedure may not be outweighed by the attendant hazards.* The present study of cerebral hemodynamics and metabolism during acute and relatively prolonged blood pressure reduction was undertaken in hopes that it might yield pertinent information concerning the above problem.

Method

The 21 subjects of the present study were hospitalized patients of various age groups, in most instances having hypertension.

Scheinberg and Stead's modification[3] of the Kety and Schmidt procedure[4] for the determination of cerebral blood flow (CBF) was applied in this study. The gas mixtures utilized were those described by Kety.[4] Blood oxygen was determined by the manometric technique of Van Slyke and Neill.[5] Mean arterial blood pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer.[6] The cerebral oxygen consumption ($CMRO_2$) and cerebral vascular resistance (CVR) were calculated as follows:

$$CMRO_2 \text{ (cc. } O_2\text{/min./100 gm. brain)} = \frac{CBF \times (A-V)O_2}{100}$$

where

$(A-V)O_2$ denotes arteriovenous oxygen difference.

$$CVR \text{ (mm. Hg/cc. blood/min./100 gm. brain)} = \frac{MAP}{CBF}$$

After control studies were made, prolonged blood pressure reduction was induced by the continuous administration of 0.2% solution of trimethaphan camphorsulfonate (Arfonad). Cerebral studies were repeated after periods ranging from 32 to 86 minutes of relative hypotension. In 10 cases, cerebral arteriovenous oxygen differences were determined during the first 10 minutes of blood pressure reduction.

Results

The effects of acute blood pressure reduction on the cerebral arteriovenous oxygen difference of 10 subjects are presented in Table 1 and are compared with control values and with determinations made after relatively prolonged blood pressure reduction. It is evident that there were small but nevertheless significant ($P < 0.01$) increases in cerebral arteriovenous oxygen differences within the first 10 minutes; these values had returned toward control levels when determined after 32 to 86 minutes of continued trimethaphan camphorsulfonate administration, although the levels of reduced blood pressure had been maintained essentially unchanged.

Table 2 compares findings during relatively prolonged blood pressure reduction with control values in 21 subjects, including those presented in Table 1. Prolonged blood pressure reduction of moderate degree was found to produce no significant change in mean cerebral blood flow or cerebral oxygen

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* References 1 and 2.

TABLE 1.—*Effects of Acute and Prolonged Blood Pressure Reduction on Cerebral Arteriovenous Oxygen Difference*

Case	Age, Yr.	MAP*			Time, Min.		AVO_2*		
		C	A	P	A	P	C	A	P
10	45	208	123	112	9	42	4.07	4.98	4.70
20	80	122	65	55	5	39	4.54	5.60	6.58
12	43	193	90	111	4	48	7.70	9.54	8.61
14	43	160	116	104	4	52	2.55	3.21	2.77
5	56	92	42	60	8	86	6.83	9.02	7.40
15	55	192	100	98	7	74	6.79	8.03	7.48
21	69	155	90	105	5	32	7.77	8.85	6.46
16	42	185	108	96	4	64	3.54	5.34	3.52
17	34	204	120	115	8	34	6.08	8.00	6.95
18	41	202	124	112	9	38	6.38	7.03	6.94
Mean values									
	51	171	98†	97	6	51	5.63	6.96†	6.14

* MAP, mean arterial blood pressure in mm. of Hg; AVO_2, arteriovenous oxygen difference in vol.%; C, control; A, acute; P prolonged.
† Significant; $P < 0.01$.

TABLE 2.—*Effects of Prolonged Blood Pressure Reduction on Cerebral Hemodynamics and Oxygen Consumption*

Case	Age, Yr.	MAP*		AVO_2*		CBF*		CVR*		Time, Min.
		C	P	C	P	C	P	C	P	
Normal or borderline blood pressure										
1	28	111	76	5.22	5.39	63.8	50.2	1.7	1.5	42
2	56	102	62	5.67	4.76	48.2	47.9	2.1	1.3	46
3	49	90	62	4.86	4.32	43.2	49.0	2.1	1.3	46
4	59	114	56	6.48	9.22	36.6	29.7	3.1	1.9	60
5	56	92	60	6.83	7.40	58.4	58.4	1.6	1.1	86
Means	50	102	63	5.81	6.22	50.0	47.0	2.1	1.4	56
Moderate essential hypertension										
6	35	144	65	6.18	8.51	39.7	37.2	3.6	1.7	49
7	57	141	78	6.91	5.95	34.8	41.4	4.1	1.9	40
8	21	125	92	2.61	2.60	78.3	76.0	1.6	1.2	35
9	27	120	63	5.82	8.03	73.8	44.6	1.6	1.4	63
Means	35	133	75	5.38	6.27	56.7	49.8	2.7	1.6	47
Severe or malignant hypertension										
10	45	208	112	4.07	4.70	66.0	63.4	3.2	1.8	42
11	37	163	98	5.15	3.84	57.1	57.0	2.8	1.7	81
12	43	193	111	7.70	8.61	46.7	44.2	4.1	2.5	48
13	37	157	120	7.29	7.29	52.3	51.2	3.0	2.3	52
14	43	160	104	2.55	2.77	94.2	86.3	1.7	1.2	52
15	55	192	98	6.79	7.48	59.0	51.7	3.3	1.9	74
16	42	185	96	3.54	3.52	88.8	78.8	2.1	1.2	64
17	34	204	115	6.08	6.95	67.5	48.2	3.0	2.4	34
18	41	202	112	6.38	6.94	51.5	45.6	3.9	2.5	38
Means	42	185	107	5.51	5.79	64.8	58.5	3.0	1.9	54
Arteriosclerosis and hypertension										
19	68	183	106	5.39	5.27	40.1	41.7	4.6	2.5	55
20	80	122	55	4.54	6.58	68.4	53.4	1.8	1.0	39
21	69	155	105	7.77	6.46	48.0	45.8	3.2	2.3	32
Means	72	153	89	5.90	6.10	52.2	47.0	3.2	1.9	42
Mean values, all subjects										
	47	151	88†	5.61	6.03	57.9	52.5	2.8	1.7†	51

* MAP, mean arterial blood pressure in mm. of Hg; AVO_2, arteriovenous oxygen difference in vol. %; CBF, cerebral blood flow in cc./min./100 gm. of brain; CVR, cerebral vascular resistance in mm. Hg/cc. blood/min./100 gm. of brain; C, control; P, prolonged.
† Significant; $P < 0.01$.

consumption. A significant compensatory diminution of mean cerebral vascular resistance was observed to accompany induced blood pressure reduction. As necessarily follows, there was no significant change in cerebral arteriovenous oxygen difference; this observation in the larger group confirms the similar finding after prolonged hypotension in the 10 subjects of Table 1. When the subjects are grouped according to probable differences in vascular tone (normal or borderline blood pressure, moderately se-

vere essential hypertension, severe or malignant hypertension, and old age with hypertension), it is seen that in each group the degree of reduction in cerebral vascular resistance was essentially the same as the proportional fall in mean arterial pressure induced by trimethaphan camphorsulfonate, although the absolute blood pressure reduction was much greater in the cases of essential and malignant hypertension.

Comment

The work of most investigators who have made quantitative measurements of cerebral hemodynamics and metabolism has shown that a large variety of procedures and drugs which produce acute blood pressure reduction elicit a cerebral vasodilator response.† In both acute and prolonged relative hypotension, as induced in the present investigation, the tendency to maintain the cerebral blood flow at adequate levels is reflected by failure of the cerebral arteriovenous oxygen difference to widen in inverse proportion to the change in blood pressure (Table 1), assuming no appreciable change in cerebral oxygen consumption. In the present series of cases, the cerebral blood flow returned practically to control values after one-half hour, although definite reduction appears to have been detected during the first 10 minutes of hypotension. Since the blood pressure levels were essentially identical in the two circumstances investigated in these studies, it must be concluded that a further diminution in the cerebral vascular resistance probably occurred as hyportension continued. It would thus appear that the mechanisms responsible for compensatory cerebral vasodilatation in the presence of blood pressure reduction may not be immediately effective in their action. It should be pointed out, however, that all except two of the subjects of Table 1 had moderate to severe hypertension.

With specific reference to subjects having malignant hypertension or cerebral atherosclerosis, the reduction in cerebral vascular resistance indicates that the cerebral vessels either are not uniformly involved in these disease states or are not completely unresponsive. A previous investigation confined to the effects of acute hypotension [9] has shown that many hypertensive and/or atherosclerotic persons do not tolerate acute blood pressure reduction of a degree proportional to that which produces no symptoms in normal subjects. It must be concluded that cerebral vascular compensation is more delayed in persons with atherosclerosis or malignant hypertension, although the present studies show that eventually it may be as effective as the compensation of persons having a presumably normal cerebral vasculature.

With precipitous reduction in blood pressure, this compensatory mechanism may not be adequate to prevent a serious reduction in oxygen delivery to high-requirement brain areas. In such instances the venous oxygen content will have fallen to minimal levels because of almost complete diffusion of its oxygen during the slowed passage of blood through the brain and the arteriovenous oxygen difference will be correspondingly widened. When such maximum utilization of blood oxygen has occurred, there is only clinical observation to indicate whether cerebral ischemia is mild or severe and the rate of blood flow can be said to have reached a critical level. The blood pressure at which this critical level is reached must vary considerably between different persons and may possibly vary in the same person at different times. This variability undoubtedly depends upon differences in tonus and reactivity of the vessel walls, as well as upon the quantitative value of oxygen requirement, the factors controlling oxyhemoglobin dissociation and oxygen diffusion, and the arterial oxygen capacity and content.

With an acute reduction of blood pressure to levels at which symptoms and signs of cerebral ischemia do not appear, compensatory cerebral vasodilation may have minimized or even prevented circulatory changes.

† References 7 and 8.

The results cast considerable doubt upon the efficacy of induced moderate hypotension in sustaining the initial reduction of bleeding tendency of cerebral tissue in neurosurgical procedures. There can be no doubt that sufficiently severe hypotension will overcome the compensatory activity of the cerebral vessels, but simultaneously the hazards of such a procedure will be greatly increased. For example, it is possible that many unhappy results of hypotensive surgery may have been averted only because the cerebral vessels have been able to overcome at least partially the local circulatory result of induced hypotension and thereby prevent undue prolongation of cerebral ischemia. It is doubtless true that tissues other than the brain which usually do not adjust to hypotension by vasodilatation may bleed to a lesser extent while blood pressure reduction is maintained, but the possibility of postoperative secondary hemorrhage remains.

Summary

Cerebral hemodynamics and metabolism were studied in 21 subjects, most of whom had varying degrees of hypertension, during the initial (acute) and prolonged phases of blood pressure reduction induced by means of intravenous trimethaphan camphorsulfonate (Arfonad). Initial widening of the cerebral arteriovenous oxygen difference in 10 subjects indicated that cerebral vasodilatation was probably not able to maintain the preinfusion rate of cerebral blood flow in the face of acutely reduced blood pressure; narrowing of the cerebral arteriovenous oxygen difference while relative hypotension was maintained indicated that progressive cerebral vasodilatation occurred and was able in time to restore the cerebral blood flow to prehypotension levels.

Measurement of cerebral blood flow and cerebral vascular resistance in 21 subjects during prolonged blood pressure reduction confirmed the indication that the cerebral vasculature is eventually able to compensate almost completely in maintaining the cerebral blood flow in spite of moderate blood pressure reduction. It is evident that the proportion of blood pressure reduction rather than the absolute value is an important factor in influencing the cerebral blood flow. With sufficiently severe hypotension (relative to a subject's usual level of blood pressure) the compensatory activity of the cerebral vessels can be overcome, but attendant hazards probably contraindicate blood pressure reduction of such degree. Induced hypotension controlled within safe limits would appear to be of little value in effecting hemostasis of cerebral tissue.

Mr. William K. Young, Miss Marie D. Negron, and Miss Julia V. V. Johnson gave technical assistance.

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Experiences with a Sphincter-Preserving Operation

Its Use in the Treatment of Carcinomatous Polyp of the Rectum

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The pull-through operation described by Swenson and Bill[1] for the treatment of Hirschsprung's disease has been able to preserve the anal sphincter with continence. Welch and Rheinlander[2] have adapted Swenson's operation to the treatment of malignant disease of the upper rectum and lower sigmoid, found approximately 14 to 16 cm. or more proximal to the anal margin. At times anterior resection for the treatment of carcinoma of the rectosigmoid may be inadequate because of the technical difficulty of getting sufficiently distal to the tumor and performing an anastomosis deep in the pelvis.

There have been a group of cases (three) with adenomatous polyp of the rectum with malignant changes approximately 3 to 5 in. from the anal margin that we have felt should be resected but with preservation of the rectal sphincter. The performance of an extremely low anterior resection in these cases is technically difficult. Instead, we have employed a modification of the Swenson operation in these instances with gratifying results.

Operative Technique: Pull-Through with Preservation of Anal Sphincter

Under spinal or general anesthesia the patient is placed in lithotomy position and simultaneously prepared and draped for the abdominal and perineal phases of the operation. The legs are then lowered to a 30-degree angle during the abdominal portion of the operation.

A left paramedian muscle-splitting lower abdominal incision extending from the pubic symphysis to 2½ in. above the umbilicus is performed. The abdomen is explored for evidence of metastasis and other pathology. The peritoneal contents are walled off from the left colon with pads, and the peritoneal reflection on both sides of the sigmoid colon is incised. The peritoneal incision is carried anteriorly separating the sigmoid from the urinary bladder in the male or from the uterus in the female. The ureters are then identified, and the superior hemorrhoidal vessels are ligated and incised just above the level of the bifurcation of the aorta. The pelvic colon is then mobilized by sharp and blunt dissection. The middle hemorrhoidal vessels are severed, and the colon must be thoroughly mobilized down to the levator ani and perineal muscles. The mesentery of the sigmoid colon is divided and ligated and the sigmoid colon severed above a distally placed clamp. The surgeon must be certain of the blood supply to the proximal end of the sigmoid colon. The rectum is severed approximately 1 cm. above the levator ani muscles. A nonabsorbable surgical (silk) suture is placed at each angle of the rectum. The patient is now placed in true lithotomy position, and the operation moves to the perineum. A clamp is inserted through the anus and the angle nonabsorbable surgical (silk) sutures grasped in the clamp. By gentle traction the anus is everted on to

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the perineum. Nonabsorbable surgical (silk) sutures are taken in the angles of the severed sigmoid, and these are fed into a clamp passed into the peritoneal cavity through the everted anus. By gentle traction the end of the sigmoid colon is pulled through the everted anus on to the perineum. A single layer interrupted anastomosis of the sigmoid to the anus with 00 Atraumatic silk going through all layers of proximal and distal bowel is then performed with ease and accuracy on the perineum. The bowel is replaced in the peritoneal cavity by gentle traction on the sigmoid colon from the abdominal side. A complementary tube cecostomy is performed, and the tube makes its exit from a stab wound in the right lower quadrant. No attempt at reperitonealization of the pelvis is done. A drain is placed in the pelvis and emerges from the lower angle of the abdominal incision. The incision is closed and a dry sterile dressing applied.

Report of Cases

CASE 1.—A 41-year-old white man was admitted to Montefiore Hospital on June 7, 1954, with complaint of intermittent rectal bleeding with and without bowel movements for the past five years. The bleeding had increased in the previous few months, but there has been no pain, constipation, weight loss, or other gastrointestinal complaints. Past history was unremarkable. In the family history the patient's mother died of cancer of the rectum. Physical examination including rectal examination was entirely negative. Hemoglobin level was 14 gm.; red blood cells, 4,850,000. Sigmoidoscopy revealed a cauliflower polyp 2×2 cm. on the posterior wall of the rectum, 5 in. above the anal verge. The polyp was removed with a snare and the base coagulated with electrocautery. The pathologic examination of the specimen revealed an adenocarcinoma arising in an adenomatous polyp of the rectum with invasion of the stalk of the polyp by nests of adenocarcinoma cells. The patient refused to have a colostomy but consented to surgery, if rectal function was preserved.

The patient was prepared for colon surgery with neomycin for 48 hours, and on June 30, 1954, he was operated upon. The sigmoid and rectosigmoid were mobilized, and in order to get well below the site of the polyp the anal canal had to be resected down to the level of the levator muscles. An intra-abdominal anastomosis was attempted, but it could not be performed in the extremely narrow pelvis. It was decided to evert the remaining anal canal through the anus, pull the end of the sigmoid colon through the everted anus, and do the anastomosis on the perineum. This was done with ease, and a complementary loop transverse colostomy was done. Postoperatively the patient had a mild degree of ileus for three days. The colostomy functioned on the fourth day. The wound healed, and patient was discharged on the 13th day.

The pathological examination of the resected specimen revealed segments of colon with an ulceration 2.5 cm. in greatest diameter. On microscopic study the ulcer did not contain carcinoma, and no carcinoma was found in any of the tissue submitted.

The patient was readmitted on August 8, 1954, for closure of the colostomy—approximately five and one-half weeks postoperatively. In the interim he had been free of complaints and gained 6 lb. On rectal examination there was good sphincter tone. On August 9, 1954, the transverse colostomy was closed. His postoperative course was relatively benign. He had some diarrhea on the fifth and sixth days, which was controlled with paregoric. There was good sphincter control. The wound healed and patient was discharged on the 12th day.

CASE 2.—A 52-year-old white woman was admitted to Montefiore Hospital for the first time on Sept. 19, 1954, with complaint of constipation of one year's duration and slight streaking of blood with bowel movements during previous six months. Sigmoidoscopy revealed a 2×1 cm. polyp 4½ in. from the anal verge. The remainder of the physical examination was unremarkable and the barium enema showed no other polyps or disease. Hemoglobin level was 13 gm.; red blood cell count, 4,870,000; urinalysis, entirely negative; blood-urea nitrogen, 14.2 mg. per 100 cc.; F.B.S., 118. The polyp was removed from below and the base coagulated with electrocautery. The microscopic examination of the specimen revealed an adenomatous polyp of the rectum.

The patient remained well for five months and had a recurrence of rectal bleeding with bowel movements in February, 1955. Sigmoidoscopy again revealed a polyp 4½ in. from anal verge. Repeat barium enema was negative for further polyps or disease. Hgb. was 13.5 gm.; R.B.C., 5,100,000. On Feb. 18, 1955, the polyp was again removed from below with a snare and electrocautery. The pathology examination revealed an adenomatous hyperplastic polyp of the rectum with malignant change. In the zone of malignant change this appeared localized to the glands and showed no evidence of invasion of the underlying stroma.

The patient was operated upon on March 1, 1955,

and the involved segment of rectosigmoid and rectum was excised, with performance of the above described pull-through operation. The pathological examination of the specimen revealed a 0.6×0.3 cm. ulceration in the mucosa, with replacement of the submucosa and superficial portion of the underlying musculature by granulation tissue and acute and chronic inflammatory cellular infiltration. There was no evidence of tumor cells in the bowel, and the mesenteric lymph nodes showed no microscopic abnormalities. Postoperatively the patient had spontaneous bowel movements on the sixth day, and the cecostomy tube was removed on the ninth day. The patient had good anal sphincter control and was discharged on the 13th postoperative day.

CASE 3.—A 46-year-old white woman was admitted to Montefiore Hospital on April 10, 1955, with the chief complaint of rectal bleeding three weeks before admission. The patient was in good health until she noted an episode of rectal bleeding during a bowel movement. She sought medical aid, and barium enema and sigmoidoscopy revealed a polypoid mass in the rectosigmoid 5 in. from anal verge. Systemic review and past history were unremarkable, except for a total hysterectomy and unilateral oophorectomy one year previous to her present illness. Physical examination was entirely unremarkable. Hgb. 11.5 gm.; R.B.C., 4,190,000; W.B.C., 7200; polymorphonuclear leucocytes 56%, lymph 35%, one eosinophile, one basophile, and seven monocytes. Urinalysis was negative. On April 12, 1955, the patient was operated upon, and the sigmoid, rectosigmoid, and anal canal down to 1½ in. from the anal sphincter were resected, performing the above described pull-through operation. The pathology report revealed an hyperplastic polyp of the colon with malignant changes but no involvement of the base of the polyp and no lymph-node metastasis.

The patient had a spontaneous bowel movement on the sixth postoperative day. Her wound healed per primam, and she was discharged on the 16th postoperative day.

Comment

Follow-up of these three cases is too short to determine whether or not this procedure is curative. Insofar as there are no metastatic lymph nodes, it is reasonable to expect that a cure may be obtained. It has been gratifying to find that sphincter control is preserved in all these cases. The major complaint is moderate constipation. Digital examination of the rectum is performed once monthly in order to detect and treat the late appearance of rectal stricture.

It is our feeling that anterior resections, which were rather popular a few years ago for the treatment of cancer of the rectosigmoid and upper rectum, failed at times because the operator was constantly concerned with technical difficulties in performing an anastomosis low in the pelvis. This led too often to an inadequate excision of rectal tissue below the limits of the cancer. As a result local recurrence at the line of anastomosis was not uncommon. With the above technique there need be no difficulty in reestablishing continuity of the left side of the colon, and at the same time one is able to go 2 to 3 in. below the cancer and thus prevent local reoccurrences. This operation should not be used to replace the abdominal perineal resection with permanent colostomy for carcinoma of the rectum below the peritoneal reflection.

A third possible application of this procedure is in the palliative treatment of cancer of the mid and upper rectum with known metastasis. Sphincter control can be preserved, and at the same time the source of bleeding, partial obstruction, fistula formation, and infection is eliminated.

A subsequent report dealing with the latter two indications will be forthcoming.

Summary

1. Three cases of adenomatous polyp of the rectum with carcinomatous changes treated by a sphincter-preserving pull-through operation are presented.

2. The application of this operation to the treatment of carcinoma of the rectosigmoid and upper rectum as a definitive and a palliative procedure is discussed.

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The Clinical Significance of Air and Barium in the Biliary Tract

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The presence of air or barium in the biliary tract indicates either an internal biliary fistula or regurgitation through an incompetent sphincter of Oddi. The finding of air in the biliary tract assumes special significance in the presence of small-bowel obstruction. In such a case the diagnosis of gallstone ileus is very strongly suggested, even though no calculus is visible. Within the past year we have seen six patients who had either air or barium in the biliary tract. One patient had a cholecytocolic fistula, one had a cholecystoduodenal fistula; in one patient there was regurgitation through an incompetent sphincter of Oddi secondary to a chronic pancreatitis, in two cases the cause was not determined anatomically, and in one patient a cholecystojejunostomy had been performed one year previously for carcinoma of the ampulla of Vater.

Incidence, Etiology, and Significance

Spontaneous internal biliary fistulas are among the least common complications of gall-bladder disease. The vast majority of operations on the biliary tract are for chronic cholecystitis with calculi or for acute exacerbations of chronic cholecystitis. Common-bile-duct calculi are said to be present in 20% of patients who have calculi in the gall bladder,[18] but in large operative series internal biliary fistulas have been reported in only 1.2% to 5%.* Waggoner in 1949 reviewed 819 cases previously reported in the literature and found that 51% were cholecystoduodenal, 21% cholecystocolic, and 19% choledochoduodenal.[14] Most of these cases were diagnosed either at operation or at autopsy. Other types of spontaneous internal biliary fistulas include the following: biliary-gastric, interbiliary, between the biliary tract and jejunum, ileum, right renal pelvis, pericardium, portal vein, hepatic artery, and the bronchial tree.†

The preoperative diagnosis of internal biliary fistula is based on the demonstration of air or barium in the biliary tract. Prior to 1941, only 90 cases were diagnosed radiologically. Scott and co-workers[12] reviewed the significance of gas and barium in the biliary tract and found 181 cases reported in the literature by 1951. This series constituted a literature review according to the radiological diagnosis—not all the cases were verified by operation or autopsy. It was believed that regurgitation through the sphincter of Oddi was responsible in 25 cases. In 57 cases a cholecystoduodenal fistula was present, in 26 a choledochoduodenal fistula, in 20 cases a cholecystocolic fistula, in four a cholecystogastric fistula, in four a biliary-bronchial fistula, and one each a cholecystoduodenocolic, choledochocolic, and cholecystojejunal fistula. Thirty-five cases demonstrated this finding postoperatively (cholecystoduodenostomy 13, cholecystogastrostomy 16, choledochoduodenostomy 6.) In seven cases the cause was undeterminable. In their own series of 10 cases 6 represented regurgitation through the sphincter of Oddi; 2

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* References 2 and 3.

† References 1 and 2.

spontaneous internal biliary fistulas (cholecystoduodenal with a carcinoma of the gall bladder and cholecystogastric), and 2, postoperative (cholecystoduodenostomy for carcinoma of the pancreas and cholecystogastrostomy for pancreatitis).

The commonest cause of an internal biliary fistula is erosion of a gallstone into an adjacent viscus, commonly the duodenum or the colon. An acute exacerbation of chronic cholecystitis may lead to a pericholecystic abscess which subsequently erodes into the duodenum or colon. Another mechanism is direct erosion of a gallstone through the gall bladder and an adjacent viscus which had become adherent in a previous acute episode.[5] These fistulas are due to primary disease of the biliary tract. However, about 6% of internal biliary fistulas are due to walled-off perforations of a duodenal ulcer with secondary erosion of the biliary tract.[14] Such fistulas are usually choledochoduodenal. Choledochoduodenal fistulas, however, may also be due to erosion of a calculus impacted in the common bile duct, although this appears to be a more unusual cause, according to the more recent literature.‡ The history of antecedent jaundice in the presence of a choledochoduodenal fistula favors the erosion of an impacted common duct calculus, although even jaundice may be due to a penetrating ulcer. If there is no history of jaundice, a primary duodenal lesion should be suspected.[2]

One of the complications of internal biliary fistulas is gallstone ileus. Lichtman reports that 0.4% to 5% of cases of intestinal obstruction are due to gallstones. He further states that a calculus more than 25 mm. in diameter will probably cause symptoms. The usual site of obstruction is the terminal ileum.§ Calculi large enough to cause intestinal obstruction usually enter the gastrointestinal tract by perforation into the duodenum. A typical triad of findings in some such cases is (1) distended small bowel, (2) gallstone in the small intestine, and (3) air in the biliary tract.‖

McLaughlin and Raines reviewed the literature and found a total of 19,692 cases of intestinal obstruction, with 366 due to gallstones, an incidence of 1.9%. The mortality previously reported in the literature is close to 50%, although they reported five cases with no mortality. If on exploration a calculus is found impacted in the small bowel, simple enterotomy and removal of the calculus is sufficient, provided the bowel is not gangrenous.[10] However, the surgeon must be alert to the presence of a second calculus, especially if the calculus is faceted. Slowly developing incomplete small intestinal obstruction (up to seven days) is said to be characteristic of gallstone ileus.[7]

The presence of gas or air in the biliary tract usually indicates either a gas-bacillus infection or an internal biliary fistula. According to the literature, air is not often found without a fistula, although in one of the cases reported below both air and barium were present without a fistula. In the absence of air but with the biliary tract outlined by barium after a barium meal, there may be either a fistula or an incompetent sphincter of Oddi, but the former is commoner.[11]

Poppel[11] has prepared a tabulation of the commoner causes producing an incompetent sphincter of Oddi with air, gas, or barium in the biliary tract without a fistula. These include (1) adhesions producing traction on the sphincter (*a*) following surgery in the region, (*b*) with intra-abdominal abscesses, (*c*) with pancreatitis, (*d*) with perforated duodenal ulcer, and (*e*) with cholecystitis and pericholecystitis; (2) tumors producing induration of the sphincter and thus keeping it patent, temporarily at least, (pancreatic, gastric, colic, and Vaterian); (3) marked antiperistalsis of the duodenum; (4) patency of the sphincter of Oddi following passage of common-duct stones (patulous sphincter); (5) disturbance of the innerva-

‡ References 16 and 17.

§ References 9 and 13.

‖ References 8 and 16.

tion with dilatation of the sphincter (this is questionable); (6) biliary-tract infections (nonascending); (7) drug effects, as after administration of atropine sulphate, and (8) ascending gas-forming infections.

Report of Cases

CASE 1.—This 63-year-old white woman was admitted on June 19, 1954, with a two-week history of pain in the left lower quadrant of the abdomen and diarrhea consisting of 15 to 20 mucoid, small brown stools daily. She had had occasional nausea, vomiting, and moderate anorexia. There had been a 10 lb. weight loss. She gave no previous history of gall-bladder disease. During a complete investigation it was noted that the gall bladder and biliary tract were outlined by air, although barium did not enter the biliary tract during either barium enema or upper gastrointestinal series. During this time she developed right upper quadrant pain,

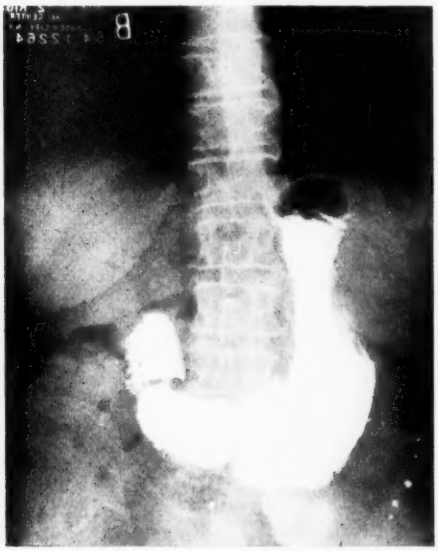

Fig. 1 (Case 1).—Air outlines the common and major hepatic ducts in this patient with a cholecystocolic fistula. No barium entered the biliary tract during this upper gastrointestinal series or a barium enema.

jaundice, chills, and fever. In view of the striking symptoms of diarrhea and tenesmus and the demonstration of air in the biliary tract, the preoperative diagnosis of cholecystocolic fistula was made. At operation a fistula was found between the gall bladder and the proximal portion of the transverse colon. The gall bladder was small and fibrotic and contained calculi, as did the common duct. A cholecystectomy was performed, the fistulous opening into the colon closed, and the common duct calculi removed, and she made an uncomplicated recovery. She has remained well more than one year postoperatively.

CASE 2.—This 69-year-old woman was admitted on Jan. 15, 1955, with a five-day history of right upper quadrant pain, anorexia, nausea, and vomiting. There was no past history of fatty-food intolerance. On examination she had a 10 to 15 cm. tender, smooth, movable right upper quadrant mass. The bowel sounds were hypoactive. Roentgenograms of the abdomen showed a few loops of distended small intestine on the left side of the abdomen, consistent with either a mechanical obstruction or paralytic ileus. (Subsequently, on reviewing the films it was evident that there was air in the biliary tract.) A cholecystostomy was done under local anesthesia, since she was in congestive heart failure. At operation the gall bladder was gangrenous with a perforation partially walled off by the omentum. Biopsy of the gall bladder revealed adenocarcinoma, type 2. She did poorly postoperatively, developed bronchopneumonia, and died on the sixth postoperative day. At autopsy she was found to have a cholecystoduodenal fistula, a gallstone impacted in the midjejunum, with perforation of the jejunum and a generalized peritonitis which obviously was the cause of death.

Fig. 2 (Case 2).—Air outlines a portion of the biliary tract on this roentgenogram of the abdomen. This patient had a cholecystoduodenal fistula.

CASE 3.—This 38-year-old white man was readmitted on May 21, 1954, because of polyuria, polydypsia, and weight loss. He had been previously admitted and explored on Nov. 26, 1953, because of epigastric pain and vomiting, with the preoperative diagnosis of pancreatitis. At exploration evidence of massive pancreatitis was found, with multiple areas of fat necrosis. He recovered and did fairly well until the present admission. His diabetes, which had appeared one week prior to admission was controlled satisfactorily. Upper gastrointestinal series demonstrated air and barium in the biliary tract, which was thought to be secondary to an active duodenal ulcer. During this admission, he developed jaundice which had the biochemical features of serum hepatitis. His course progressively deteriorated; he had an episode of upper gastrointestinal hemorrhage, developed bronchopneumonia, and died on Aug. 5, 1954. At autopsy there was a 15 by 8 by 3 cm. encapsulated retroperitoneal abscess containing milky fluid on the left side between the quadratus lumborum and the psoas muscles. There were numerous calculi in the gall bladder, but the entire biliary tract was carefully dissected and there was no obstruction, calculus or fistula involving the extrahepatic biliary system. There was, however, a common channel for a distance of 0.8 cm. for the common bile duct and the pancreatic duct. There was no evidence whatever of gastric or duodenal ulcer, and the cause of the gastrointestinal hemorrhage was never determined.

Fig. 3 (Case 3).—Barium entered the common duct during this upper gastrointestinal series.

Fig. 4 (Case 3).—Note the air in the biliary system. This patient had a chronic pancreatitis, and at autopsy no fistula was found.

CASE 4.—This 79-year-old white man was admitted on April 30, 1954, because of a recent injury to his left arm. During his hospitalization he had an episode of rectal bleeding. Proctoscopic examination was negative, as was barium enema. Gastrointestinal series on April 27, 1954, demonstrated a large barium shadow in the area of the duodenal cap along with barium in the common, cystic, and hepatic ducts, which was felt to be indicative of a fistula between the duodenum and biliary tract. He was asymptomatic until 10 months later when he had an episode of massive upper gastrointestinal hemorrhage with hematemesis. This stopped spontaneously. A repeated gastrointestinal series was unsatisfactory because of his disturbed mental state and he had to be transferred to the County Mental Institution. At the time of transfer, because of his senile psychosis, he had no detectable gastrointestinal symptoms.

CASE 5.—This 80-year-old white woman was admitted on March 2, 1955, with a four-day history of right upper quadrant pain radiating to the back and to the right shoulder. She had had chronic fatty-food intolerance for many years. On examination there was an 8 to 10 cm. tender right upper quadrant mass. Preoperative roentgenograms showed no evidence of air in the biliary tract. A cholecystostomy was done under local anesthesia. The postoperative impression was gangrene and empyema of the gall bladder. Despite the fact that she pulled out the cholecystostomy catheter on the

third postoperative day she made an uneventful recovery. Two weeks postoperatively an upper gastrointestinal series revealed a normal stomach, duodenum, and small bowel. However, there was filling of the biliary radicles of the liver and of the common duct, apparently from the second portion of the duodenum. Subsequently, a gallbladder series and intravenous cholangiogram demonstrated air in the biliary tract. She had

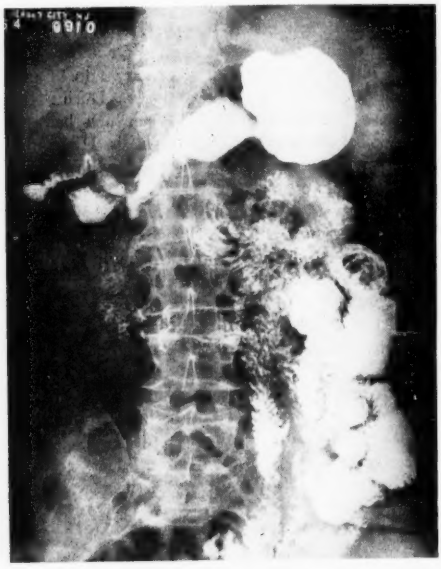

Fig. 5 (Case 4).—The common duct, cystic duct, and gall bladder are filled with barium. There is also air in the common hepatic duct and the tributaries of the right hepatic duct.

Fig. 6 (Case 4).—The retroduodenal portion of the common duct is well outlined. This patient subsequently had an episode of massive hematemesis.

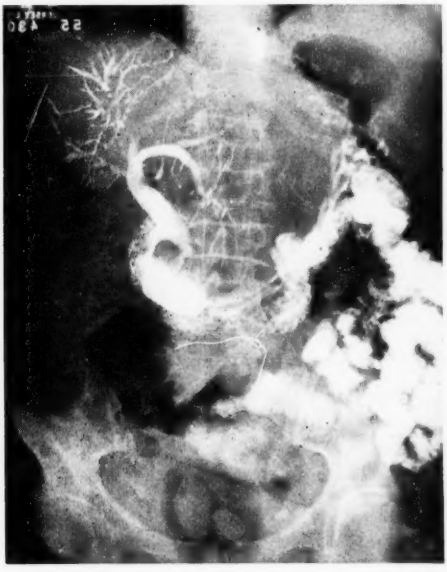

Fig. 7 (Case 5).—The entire biliary tree is filled with barium.

Fig. 8 (Case 5).—Note the tremendously dilated common duct visualized during an unsuccessful intravenous cholangiogram.

never been jaundiced, and in view of her advanced age and absence of symptoms she was discharged three weeks after cholecystostomy. She has remained well since that time.

CASE 6.—This 43-year-old white woman was admitted on Aug. 14, 1954, with obstructive jaundice. On Aug. 26, 1954, laparotomy revealed a carcinoma of the ampulla of Vater with numerous lymph-node metastases. In view of these findings a local resection of the primary tumor was performed. A T-tube was placed in the common duct with the long arm extending into the duodenum. A cholecystojejunostomy was also performed. Her postoperative course was uneventful, and after a

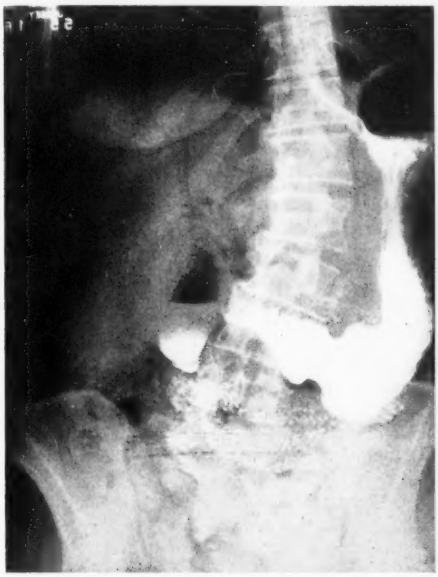

Fig. 9. (Case 6).—Barium fills the fundus of the gall bladder, and air is present in the cystic duct, common hepatic duct, and the right and left hepatic ducts. The distal common duct is abruptly occluded in this patient with an ampullary carcinoma which cannot be operated on, one year after a cholecystojejunostomy.

normal cholangiogram the tube was removed. She remained asymptomatic and gained 25 lb., until one year later when she first noted mild occasional right upper quadrant and epigastric pain. Examination at this time was essentially negative, but on Sept. 20, 1955, an upper gastrointestinal series demonstrated air and barium in the common bile duct.

Comment

The presence of air in the biliary tract enabled us to make the correct diagnosis of cholecystocolic fistula preoperatively in the first case. In this patient the diagnosis should have been considered sooner, but the appearance of unequivocal signs and symptoms of cholecystitis, common-duct obstruction, and cholangitis, together with the striking colonic symptoms of diarrhea and tenesmus, made the diagnosis fairly evident.[15] It is of interest that the diarrhea stopped during the period that she was jaundiced. We postulate that the cholecystocolic fistula served to decompress the biliary tract, that it became temporarily obstructed and she therefore became jaundiced. With reopening of the fistula large quantities of bile again appeared directly in the colon causing diarrhea and tenesmus. The original cause of the fistula was impaction of a calculus in the cystic or common bile duct with an unrecognized acute cholecystitis. We were unable to elicit a previous history of jaundice or symptoms of acute cholecystitis.

In the second case it appears likely that the original pathological process was an acute exacerbation of a chronic cholecystitis initiated by impaction of a calculus in the cystic duct. It is obvious that the x-ray findings of dilated small bowel at the time of admission, in retrospect, were due to impaction of the calculus in the jejunum. The diagnosis of gallstone ileus was not entertained, unfortunately, since the calculus was not calcified and air in the biliary tract was not recognized. The carcinoma of the gall bladder probably represented only an incidental finding in this case, although some authors believe carcinoma of the gall bladder may either produce such fistulas or cause them to persist.¶

In the third case it was felt that the patient had a duodenal ulcer. However, no evidence of either an active or healed ulcer was found, despite careful examination at autopsy. Similarly there was no fistula. The attending surgeon who had operated on this patient was most careful at autopsy to

¶ References 2 and 14.

search for such a fistula in view of the antemortem diagnosis. It appears, then, that this represented regurgitation through a sphincter which was kept patent by a fibrosing chronic pancreatitis. The presence of air in the absence of a fistula appears to be uncommon.[11]

In the fourth case the history of rectal bleeding and subsequent hematemesis suggests that the fistula was secondary to erosion of the biliary tract by a chronic duodenal ulcer. If a fistula is present we believe, on the basis of the literature, that it is choledochoduodenal.# However, verification of the cause requires anatomical demonstration either at laparotomy or at postmortem examination.

Likewise, in the fifth case it is possible that the barium regurgitated through an incompetent sphincter. There is no direct evidence of an ulcer or history of jaundice. Since air was present in the biliary tract, we are more inclined to believe that a fistula is present and that this is most probably cholecystoduodenal. However, we do not have anatomical demonstration of the lesion, and we have reported above, in our third case, the presence of air without a fistula.

In the sixth case the presence of a surgical biliary fistula continues to afford satisfactory decompression. In view of the moderately advanced stage of her disease at the time of her operation, she remains surprisingly well. It is of interest that the roentgenograms demonstrate that the distal common duct is blocked, the point of obstruction being very clearly outlined by both air and barium. We believe that this probably represents a recurrent carcinoma.

Summary

The etiology and significance of air and barium in the biliary tract are discussed.

Six cases of air or barium in the biliary tract are presented; two cases represent proved spontaneous internal biliary fistulas (cholecystocolic and cholecystoduodenal); in one case there was regurgitation through an incompetent sphincter of Oddi; in two cases the cause was undetermined; in one case a cholecystojejunostomy had been previously performed.

The preoperative diagnosis of internal biliary fistula is based on the demonstration of air or barium in the biliary tract.

In cases of small-bowel obstruction the presence of air in the biliary tract strongly suggests gallstone ileus. One such case in which this finding was not recognized, with fatal outcome, is presented.

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Primary Sarcoma of the Bronchus and Lung

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Primary sarcoma of the lung is generally conceded to be a relatively uncommon disease. Hertz (1874) denied the existence of this condition, stating that every sarcoma found in the lung had its origin elsewhere. Adler (1912), asserting that he had never seen a case of primary sarcoma of the lung, expressed astonishment at the number of cases reported in the literature. In his book on "Primary Malignant Growths of the Lung and Bronchi," published in 1912, Adler presented a review of 374 cases of primary carcinoma of the lung and 90 primary sarcomas. In 1926, Barnard pointed out that the "oat-cell sarcoma" of the lung is in reality of carcinomatous origin. Four years later, Karsner and Saphir showed that another lesion, one previously described as a "small cell or lymphosarcoma" of the lung, was of epithelial origin and therefore also a carcinoma rather than a sarcoma. Reviewing the work of Adler, with the foregoing concepts in mind, we were led to conclude that many of the cases reported as primary sarcomas were carcinomas. In 1931, Ball presented a review of the English, French, and German literature on the subject published between 1900 and 1931. He found that only 14 cases were acceptable as primary sarcomas of the lung. To these he added a case under personal observation.

Ellis (1939) noted that in a series of 7272 autopsies performed in the department of pathology of the University of Kansas Hospitals 28 (0.39%) were for primary malignancy of the lung and only 1 (0.014%) of the autopsies was for a primary sarcoma of the lung. Of the 68,404 surgical specimens received in the pathology laboratory of the Jewish Hospital of Brooklyn between 1943 and 1954, there were 8 instances (0.012%) in which primary sarcoma of the lung and/or bronchus was diagnosed. Of the 2489 autopsies performed during the same period, not one primary bronchopulmonary sarcoma was encountered.

The present study reviews the cases reported between 1944 and 1954 and an additional six cases not reported previously. In the occasional instance, reference is made to earlier work. Two cases antedating 1944 have not been included in our Tables. We have chosen not to include the works published prior to 1944 because, in reviewing this material, we were confronted by a maze of confusing material and incomplete case reports. To some extent the same criticism may be leveled at some of the case reports appearing in the present-day medical literature.

Classification

Reports in the recent literature indicate that the majority of primary sarcomas of the bronchopulmonary system fall into five categories which may be classified as follows:

1. Fibrosarcoma
2. Malignant lymphomas
   - A. Lymphosarcoma
   - B. Hodgkin's disease
   - C. Reticulum-cell sarcoma
3. Leiomyosarcoma
4. Carcinosarcoma
5. Miscellaneous sarcomas
   - A. Chondrosarcoma
   - B. Lipomyxosarcoma
   - C. Angiosarcoma
   - D. Malignant giant-cell sarcoma

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Collected Cases of Primary Bronchopulmonary Sarcoma

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
1.	d'Amato, Latienda & Pizarro (1947)	F 25	18 mo.	Cough, expectoration night sweats, loss of weight, dyspnea, elevation in temperature, wheezing	Infiltration, left upper lobe and right hilar area	.....	Hodgkin's disease	Symptomatic	Pulmonary tuberculosis and Hodgkin's disease, L.U.L. (Found at necropsy)
2.	Anlyan, Lovingood & Klassen (1950)	M 63		Asymptomatic	Area of increased density at right base	No significant pathologic changes; aspirated bronchial secretions did not show malignant cells	Lymphosarcoma	Right lower lobectomy	Tumor mass measured 8 X 4 X 4 cm.
3.	Baraldi (1946)	M 40	6 mo.	Cough, loss of weight	Infiltration of L.U.L.	.....	Fibrosarcoma	Left upper lobectomy	Well 5 mo. after operation
4.	Barani (1951)	M 57	14 mo.	Dyspnea	Round mass, L.U.L.	No endobronchial lesion; bronchial washings negative for tumor cells	Angiosarcoma	Exploration of chest (biopsy taken)	Vascular mass left upper lobe involving mediastinum and parietal pleura
5.	Bass & Reibstein (1950)	F 65	Several mo.	Epigastric pain, vomiting, loss of weight	Mass in left parahilar area	Negative	Hodgkin's disease	Exploration of chest (biopsy taken)	Infiltrative mass, L.U.L., with hilar involvement making complete removal impossible
6.	Beck & Reganis (1951)	F 47	2 mo.	Epigastric pain, loss of weight	Discrete mass, R.L.L. near costophrenic angle, 6 cm. in diameter	.....	Lymphosarcoma	Right lower lobectomy	Tumor measured 8 cm. in diameter; well 15 mo. postoperatively
7.	Behrend & Kravitz (1951)	M 25	4 yr.	Cough, chest pain, blood streaked sputum, expectoration, loss of weight, night sweats	Homogeneous density obscuring lower right hemithorax	.....	Fibrosarcoma	Removal of R.L.L. and part of adherent diaphragm	Tumor arose in cyst of lung; developed difficulty in swallowing and died 10 mo. after operation — mediastinal metastasis
8.	Bergmann, Ackerman & Kemler (1951)	M 51	1 yr.	Cough, malaise, fever, loss of weight, pain in chest	Atelectasis, R.U.L.	Papillary tumor, R.U.L. bronchus	Carcinosarcoma (Epidermoid carcinoma, Fibrosarcoma)	Right pneumonectomy	No signs of recurrence 6 yr. after operation
9.		M 56	6 wk.	Pleuritic pain, elevation in temperature, malaise, loss of weight	Right hilar mass extending into the lower part R.U.L.	Bronchoscoped 3 times (see remarks)	Carcinosarcoma (Epidermoid carcinoma, Fibrosarcoma)	Right pneumonectomy	At the time of first admission operation revealed a lesion in the lung thought to be a lung abscess; this was drained; part of the wall of the abscess was examined by the pathologist who reported same as negative for tumor tissue; patient readmitted to the hospital 2 mo. later; bronchoscopy disclosed lumen of R.U.L. filled with smooth granulation tissue; biopsy failed to show the presence of tumor tissue; a second bronchoscopy and biopsy a month later was similarly negative for tumor tissue; a third bronchoscopic biopsy 2 mo. later was reported as unclassified malignant tissue; patient well 18 mo. after the operation.

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
10.	Black (1950)	F 46	9 mo.	Cough, fever, hemoptysis, malaise	Shadow, L.L.L.	Polypoid tumor blocking L.L.L. bronchus; biopsy reported as a very cellular tumor	Fibrosarcoma	Left pneumonectomy	Died 6 yr. and 5 mo. after operation; autopsy showed mediastinal glands, bronchial stump, and pericardium contained tumor tissue
11.	Bugoslavskaya (1945)	M 38	6 mo.	Pain in shoulder, edema left arm, cough, Horner's syndrome	Opacity, L.U.L.	----------	Fibrosarcoma	----------	Autopsy 10 wk. later revealed tumor in left upper lobe and metastasis to ribs, pleurae, diaphragm, left supraclavicular, axillary and subscapular nodes
12.	Carswell & Kraeft (1950)	M 29	18 mo.	Pain in chest, dyspnea, cough, wheezing, loss of weight, hemoptysis, chills, fever	Pleural thickening with subpleural fibrosis at right apex and atelectasis L.L.L.	Bronchoscopy on two occasions negative; rebronchoscopy showed the left main bronchus occluded by a round, smooth, nonulcerated, dark red, firm tumor; biopsy was reported as fibrosarcoma	Fibrosarcoma	Left pneumonectomy	Well 7½ mo. after operation
13.	Casarini & Morone (1949)	M 43	3 mo.	Subscapular pain, cough, fever, loss of weight	Opacity of R.U.L. with partial destruction of the 2d, 3d and 4th ribs	----------	Chondrosarcoma	----------	Autopsy disclosed tumor in the right upper lobe; bilateral pulmonary silicosis; tuberculosilicosis of the hilar lymph nodes
14.	Churchill (1947)	F 45	6 mo.	Fever, pain in right shoulder, malaise	Homogeneous opacity right upper lung field	No positive findings	Malignant lymphoma	R.U. and R.M.L. resected	Well 8 mo. after operation; resected lung also showed the presence of coccidioidomycosis
15.	Cichero (1952)	M 40	4 mo.	Intermittent pain in right axillary area, cough, blood-tinged sputum, loss of weight	Circumscribed opacity in right infra-axillary area; fluid in costophrenic area	----------	Lymphosarcoma	Right pneumonectomy	Died 20 mo. after operation
16.	Cote (1945)	F 66	6 mo.	Pain in left chest, dyspnea, wheezing, cough	Opacity of left hemithorax and atelectasis of lung	Mass in terminal part of left main bronchus; biopsy reported as myxoid tumor	Fibrosarcoma	----------	Died 6 mo. later; autopsy revealed fibrosarcoma of left main bronchus; there were no metastases
17.	Curry & Fuchs (1950)	F 13	6 wk.	Cough, wheezing, mucopurulent expectoration, expectoration of a mass, hemoptysis	Negative	----------	Fibrosarcoma	None	Follow-up of patients by x-ray studies of the chest and bronchoscopy did not reveal recurrence in 4 yr.
18.	Drewes & Willmann (1953)	M 40	----	Asymptomatic	Shadow the size of a small apple in left upper thorax	----------	Lymphosarcoma	X-ray therapy; Left pneumonectomy	X-ray therapy with some shrinkage; 2 yr. later had a left pneumonectomy; well 6 mo. after operation
19.		M 9	3 mo.	Loss of weight, anorexia, malaise, vomiting, articular pains, elevation in temperature	Round mass in left retrocardiac area	----------	Fibrosarcoma	Left lower lobectomy; x-ray therapy after operation	Well 20 mo. after operation

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
20.	Dvoracek & Cermak (1952)	M 44			Right upper lobe opacity	----------	Lymphosarcoma		
21.	Efskind & Wexels (1952)	F 30	4 mo.	Elevation in temperature, pain in chest, listless	Infiltration in right upper lobe which later excavated to form a thick-walled cavity	Nonrevealing	Hodgkin's disease	Resection of right upper and middle lobes	
22.		F 22	?	Jaundice 2 yr. previously; routine x-ray of chest revealed pathology	Dense infiltration and cavitation, R.U.L.	Nonrevealing	Hodgkin's disease	Resection right upper and middle lobes	Surgery was followed by x-ray therapy; 2 yr. after operation developed infiltration of left lung; died soon thereafter
23.	Fleming & Howie (1951)	F 60	7 yr. ?	Cough, hemoptysis, elevation in temperature	Irregular infiltration, R.L.L.	----------	Lymphosarcoma	----------	Autopsy revealed a neoplasm in the right lung with stenosis of all the bronchi; diffuse lymph node involvement was also noted
24.	Fojanini & Armenio (1952)	M 26	3 yr.	Pain in left chest, loss of weight, asthenia, elevation in temperature	Opacity, R.U.L., the size of a small orange	----------	Fibrosarcoma	Right pneumonectomy	Died 4 mo. after operation
25.	Giraud, Bernard, Metras & Orsini (1947)	M $3\frac{1}{2}$	3 yr. ?	Pulmonary congestion, cough, dyspnea, since about 6 mo. of age	Cyst-like mass in R.U.L.	----------	Reticulum-cell sarcoma	----------	Autopsy revealed a reticulum-cell sarcoma within a cyst of the right upper lobe
26.	Gnassi & Price (1945)	M 47	6 mo.	Precordial pain, dyspnea, polyarticular pains, elevation in temperature, cough, expectoration	R.U.L. spherical homogeneous density	Intact bronchial mucosa	Malignant giant-cell tumor	----------	Died suddenly six months later; autopsy did not disclose any metastases
27.	Grimes, Weirich & Stephens (1954)	F 68	8 mo.	Cough, hemoptysis, exertional dyspnea, loss of weight	Area of consolidation in lower left lung	An area of neoplastic tissue was seen in the proximal portion of L.L.L. bronchus; biopsy of tumor noncontributory to diagnosis	Lymphosarcoma	Left pneumonectomy	Well 2 yr. after operation
28.		F 45		Asymptomatic	Mass in left hilar region with streaks of dense tissue extending from it into the lung tissue	Nonrevealing	Lymphosarcoma	Left pneumonectomy	Well 5 yr. after operation
29.	Heatley (1950)	M 18	1 wk.	Two years previously an asymptomatic mass was found in chest on routine x-ray study; at recent admission to hospital had cough and dyspnea	Atelectasis, R.L.L.	Smooth, red mass in right bronchus; biopsy reported as lymphoma, possibly Hodgkin's disease	Hodgkin's disease	Exploratory thoracotomy with removal of some tissue for biopsy	Biopsy was diagnosed as Hodgkin's disease
30.	Higginson & Grismer (1950)	M 24	3 mo.	Elevation in temperature, cough, fatigue, irritability, expectoration	Lobulated mass in right hilum; clouding R.L.L. by fluid	Granulomatous mass in R.L.L. bronchus; biopsy diagnosed as squamous-cell carcinoma; re-bronchoscopy and biopsy; diagnosed as Hodgkin's disease	Hodgkin's disease	X-ray therapy	Rebronchoscoped 6 mo. after x-ray therapy; there was no evidence of tumor in the bronchus at this time

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
31.	Hochberg, Grayzel, Berson & Rosenberg (1949)	F 55	4 mo.	Chronic cough (10 yr.), expectoration, hemoptysis	Circumscribed tumor in upper half of left lung field	.....	Fibrosarcoma and epidermoid carcinoma	Left upper lobectomy	Patients failed to recover after operation and died 17 hr. postoperatively; autopsy disclosed multiple benign tumors in other parts of the body
32.	Iverson (1954)	M 28		Asymptomatic	Routine chest x-ray examination revealed a rounded shadow L.U.L.	No abnormality	Fibrosarcoma	Left upper lobectomy	Neoplasm was comprised of a nodular mass in the wall of a cyst of the L.U.L.; patient well 4 yr. after operation
33.		M 60		Asymptomatic	Mass in R.U.L.	.....	Fibrosarcoma	Right upper lobectomy	Well 3 yr. after operation
34.		M 47	9 wk.	Tightness in the chest	Infiltrative lesion L.L.L.; subsequent x-rays of chest revealed mass in L.L.L.	.....	Fibrosarcoma	Left lower lobectomy with postoperative x-ray therapy	Mass recurred 6 mo. later and x-ray therapy given again; patient died 1 yr. after operation; autopsy showed recurrence in left lung and metastases to right lung
35.	Johnson, Mangiardi & Jacobs (1952)	M 52		Pain in chest, cough, night sweats, loss of weight	Dense opacity, R. U.L.	Carina deviated to right, otherwise negative; bronchial aspirate negative for tumor cells	Leiomyosarcoma	Right pneumonectomy	
36.	Killingsworth, McReynolds & Harrison (1953)	F 7	1 yr.	Cough, fever, anorexia, loss of weight, "smothering spells," pain in chest, listless	Uniform opacity of left lung	Smooth reddish mass filling lumen of left main bronchus; biopsy reported as benign bronchial epithelium; rebronchoscopy reported as the same	Leiomyosarcoma	Left pneumonectomy	Well two years after operation
37.	Kulka (1950)	F 30	3 mo.	Cough, dyspnea	.....	.....	Hodgkin's disease	.....	Patient died suddenly at home; autopsy revealed left lung, pleura, and diaphragm lined by yellowish pink nodular tissue
38.	Latienda & Itoiz (1946)	M ?	2 mo.	Pain in arm, neck, and shoulder; dysphagia, dysphonia, cough	.....	.....	Myxoliposarcoma	.....	Autopsy findings: Right hemithorax occupied by a gelatinous mass, pushing mediastinum to left; a myxomatous mass replaced the R. U. and R.M. lobes
39.	Lewis (1947)	M 14	3 mo.	Dyspnea, pain in chest, cough, expectoration	Opacity R.U.L., widening of mediastinum, displacement of heart to right	Right main bronchus filled with soft yellowish-white growth; biopsy reported as fibrosarcoma	Fibrosarcoma		
40.	Lowell & Tuhy (1949)	F 41	18 mo.	Fatigability, nervousness, anorexia, ankle edema, loss of weight, dyspnea, tachycardia, palpitation, fullness and soreness of the left side of the chest, cough	Density in left lung adjacent to the mediastinum at the level of the sixth intercostal space; left leaf of diaphragm higher than right	The left main stem bronchus and its subdivisions were displaced posteriorly as if by a mass lying anteriorly	Chondrosarcoma	.....	Autopsy findings: Mass in the left hilum extending into the pulmonary artery to within 1 cm. of pulmonary valve; the tumor mass measured 6X10 cm.

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
41.	Maier (1948)	M		Asymptomatic	Asymmetry of chest	No evidence of en-	Lymphosarcoma	Left pneumonectomy	Mass in left chest discovered

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
41.	Maier (1948)	M 50		Asymptomatic	Asymmetry of chest with narrowing of intercostal spaces on left side; heart and mediastinum displaced to left; left leaf of diaphragm elevated	No evidence of endobronchial lesion	Lymphosarcoma	Left pneumonectomy	Mass in left chest discovered during fluoroscopic examination for gastric ulcer; 19 mo. after operation there was recurrence in right lung which was treated by x-ray 7 mo. later; patient apparently well 30 mo. after operation
42.	Mass. Gen. Hosp. Conf. Case 31271 (1945)	M 65	9 mo.	Malaise, anorexia, weakness, loss of weight, edema of ankles	Circumscribed density at the base of right lung	----------	Fibrosarcoma	Right lower lobectomy	Patient died 4 wk. after operation
43.	Mishkin (1951)	F 65	2 wk.	Palpitation, dyspnea, loss of weight, malaise, elevation of temperature	Tumor in region of left side of heart	----------	Myosarcoma	----------	Autopsy findings: Tumor mass in L.U.L. measuring 20 cm. in diameter; it was well demarcated from the remainder of the lung but not encapsulated
44.	Nilsson (1951)	M 35			see remarks	----------	Fibrosarcoma	----------	1939, patient developed tuberculosis, R.U.L. 1942, a cavity developed in that lung which was treated by apicolysis; the general condition of the patient remained fair until 1946, when an x-ray of the chest disclosed a circumscribed mass in L.L.L.; in July, 1949, x-ray studies of the chest revealed metastases within the lung; patient died on Aug. 1, 1949; autopsy disclosed a round tumor in L.L.L. which was 25 cm. in diameter; the R.U.L. contained a residual tuberculous cavity
45.	Nobile (1952)	M 15	6 mo.	Pain in right side of chest, radiating into right arm; dyspnea, elevation in temperature	Round opacity in upper half of right hemithorax	----------	Reticulum-cell sarcoma	----------	Autopsy findings: Cystic mass in R.U.L. encapsulated within the lung and extending upward to involve common carotid artery, superior vena cava, and innominate artery; the inferior vena cava was also compressed by the tumor
46.	Noehren & McKee (1954)	F 61	2 yr.	Dyspnea, ankle edema, dry cough	Density at right base	----------	Fibrosarcoma	----------	Autopsy findings: In R.L.L. were firm nodular masses; the bronchial mucosa was smooth and intact
47.	Randall & Blades (1946)	M 34	2½ yr.	Cough, dyspnea, weakness, expectoration, hemoptysis	Density at right hilum; retraction of mediastinum to right and elevation right leaf of diaphragm	Smooth, rounded mass almost completely occluding right main bronchus and partly covering carina; biopsy on repeat bronchoscopy reported as low grade leiomyosarcoma	Leiomyosarcoma	First stage pneumonectomy	Autopsy findings: Circumscribed tumor in right hilar area extending into R.U.L.; tumor friable and attached to carina by a pedicle approximately 3 mm. in diameter; detached from this portion was the large friable hemorrhagic tumor enclosed within the right main bronchus proximally but extending along the upper lobe bronchus where the adjacent lung parenchyma was infiltrated; cross section of the lung and tumor disclosed an irregularly circumscribed mass 10 to 14 cm. in diameter limited to the R.U.L.

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
48.	Ransdell, Bailey & Ellison (1951)	M 37	5 mo.	Soreness of the chest, hemoptysis, night sweats, expiratory wheeze, cough, dyspnea, anorexia, loss of weight, malaise	Small, ill-defined, mass projecting from right upper mediastinum	An essentially normal bronchial tree; bronchial washings were not contributory to diagnosis	Reticulum-cell sarcoma in the wall of a pulmonary cyst	Right upper lobectomy	Postoperative x-ray therapy (4,500 r) was given to the right superior mediastinum; well 3 mo. after operation
49.	Sarokhan & Morrison (1953)	M 70	2 mo.	Cough and expectoration	Density of lingular segment of L.U.L.	No significant pathology	Lymphosarcoma	Left upper lobectomy	Patient died 5 wk. after operation
50.	Sherman & Malone (1950)	M 57	?	Cough and pain in the chest	Mass in right lung	----------	Myosarcoma	Resection of R.M. and R. L. lobes	Well 4 mo. after operation
51.		F 67	2 mo.	Cough, substernal pain	Mass in the left hilar area	Tumor, the biopsy of which was reported as myosarcoma	Myosarcoma	----------	Patient refused surgery
52.		F 6	?	Frequent attacks of pneumonia; dyspnea, cough	Obstruction to right main bronchus	Carina replaced by an irregular friable mass which extended into both major bronchi; biopsy reported as myosarcoma	Myosarcoma	X-ray therapy	Patient was unable to take the x-ray therapy; died 3 mo. later
53.	Soulas (1945)	M 32	4 mo.	Dyspnea, hemoptysis, elevation in temperature, cough	Right paramediastinal shadow	Right stem bronchus is obstructed by a red, smooth tumor mass; biopsy was reported as lymphogranulomatosis	Hodgkin's disease	X-ray therapy	Patient rebronchoscoped a second and third time; the biopsy on the third occasion was reported as Hodgkin's disease
54.	Spatt & Grayzel (1947)	F 34	3 mo.	Hemoptysis, pain in chest, cough	Small egg-shaped mass in the right chest in lower lung field	Evidence of suppuration of R.L.L.	Lymphosarcoma	Right lower lobectomy	Well 14 mo. after operation
55.	Storey (1952)	M 39	?	Pain in the chest, cough, dyspnea, expectoration	Mass occupying the lower 2/3 of the left chest posteriorly	A tumefaction is present in the proximal portion of L.L.L. bronchus; biopsy was reported as fibrosarcoma	Fibrosarcoma	Left pneumonectomy	Died 9 mo. after operation; metastases
56.		F 62	6 mo.	Cough, expectoration, loss of weight, fatigue	Atelectasis of basilar segment, R.L.L.	Large pedunculated, fungating mass in the lumen of the intermediate bronchus; biopsy was reported as suspicious of malignancy	Fibrosarcoma	Right pneumonectomy	Died 18 mo. after operation; metastases
57.		F 41	5 mo.	Chills, fever, malaise	Pneumonia of right midlung field	Bronchoscopic biopsy was reported as a moderately cellular fibroma	Fibrosarcoma	Resection of the R.M. and R.L. lobes	Well 15 mo. after operation

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
58.	Stout & Himadi (1951)	M 41	4 days	Cough, pain in chest and shoulder	Spherical mass in R.L.L.	Negative	Fibrosarcoma	Enucleation from lung followed by x-ray therapy	Died 1 yr. after operation
59.		M 57	8 mo.	Cough, hemoptysis, pain in chest	Round shadow in R.L.L.	Negative	Fibrosarcoma	Resection of the R.L.L.	No recurrence 2 yr. after operation
60.	Taylor & Rae (1952)	M 69	2 mo.	Cough, malaise, elevation in temperature	Atelectasis of R.M.L. and R.L.L.	Right main bronchus plugged by a brownish necrotic mass; biopsy reported as inflammatory	Carcinosarcoma	Right pneumonectomy	Second bronchoscopic biopsy was reported as sarcoma possibly of neurogenic origin; patient well 3 yr. after operation but is dyspneic
61.		M 57	2 mo.	Dyspnea, pain in the chest, hemoptysis, loss of weight	Atelectasis of left lung	Mass in left main bronchus; biopsy reported as bronchial mucosa	Carcinosarcoma	----------	Autopsy findings: Pedunculated tumor entirely endobronchial
62.	Tenczar (1953)	F 43	4 wk.	Swollen right parotid gland; swelling of small joints, fever, chills, pain in chest, dyspnea, cough, blood-tinged sputum; swelling of hands, knees and ankles	Slight increase in right hilum density	----------	Lymphosarcoma	Symptomatic	Patient was admitted to the hospital 7 times in less than 2 ½ yr. Autopsy findings: Lymphosarcoma of all lobes of lungs and of the cervical, paratracheal and parapancreatic lymph nodes.
63.	Verstraeten & Boels (1951)	F 34	3 ½ yr.	Hemoptysis, pain in chest	Round homogeneous opacity, L.U.L.	Negative	Fibrosarcoma	Left pneumonectomy	Patient was seen for the first time on 3/3/47; at this time she had a tumor in the L.U.L.; 18 mo. later the tumor had increased in size; on 12/7/50 she was seen again (3 ½ yr. after the first examination) with the same symptoms; x-ray of the chest at this time showed further increase in size of the tumor; at this time the tumor was removed
64.	Watson & Anlyan (1954)	M 57	10 mo.	Pain in chest, dyspnea, productive cough	Soft-tissue shadow in the right lower lung field suggestive of a benign cyst of the right middle lobe	Reddening of the bronchial mucosa of the middle branch of the right lower lobe bronchus; biopsy revealed benign epithelium	Leiomyosarcoma	Resection of R.M.L. and R.L.L.	The tumor removed was within the R.M.L. and involved the R.L.L. by continuity; patient well 6 yr. after operation
65.		F 63	1 mo.	Dyspnea, productive cough, pain in chest	Large rounded density in L.U.L.	----------	Leiomyosarcoma	Tumor removed	Sputa studies were negative for tumor cells; patient free of disease for 5 yr. after operation
66.		F 66	----------	Pain in chest, cough	Circumscribed mass adjacent to the left of cardiac border	No endobronchial lesion; bronchial secretions revealed atypical cells	Leiomyosarcoma	Exploratory thoracotomy; x-ray therapy	Patient died 9 mo. after exploration of the chest, from extension of the disease
67.		M 66	?	Weakness and constipation	An irregular lobulated density in right costophrenic angle	Normal tracheobronchial tree; bronchial washings negative for neoplastic cells	Leiomyosarcoma	Local excision	----------

Case	Author	Sex and Age	Duration of Illness	Symptoms	Roentgenographic Findings	Bronchoscopy	Histopathology	Therapy	Remarks
68.	Watson & Anlyan (1954)—Continued	M 4	3 mo.	Cough, dyspnea, orthopnea, hemoptysis	Displacement of mediastinum to right, emphysema of left lung	Right main bronchus filled with a reddish tumor; biopsy revealed spindle-cell sarcoma, possibly leiomyosarcoma	Leiomyosarcoma	Exploration of chest	Died during the operation
69.		F 67	2 yr.	Cough, dyspnea, expectoration, pain in chest	Large, round mass in paravertebral area of inferior left hemithorax	Blood in bronchial lumen; biopsy of the region of the left lower lobe bronchus was reported as myosarcoma	Leiomyosarcoma	Patient refused surgery	Sputum negative for neoplastic cells; patient died 2 yr. later
70.	Weissman & Christie (1951)	M 52	1 yr.	Cough, loss of weight, weakness, dyspnea	Dense mass in the middle of left lung field	Smooth narrowing of the bronchi to the L.U.L.	Lymphosarcoma	Left pneumonectomy	.....
71.	Yardumian & Myers (1950)	M 52	2 wk.	Malaise, weakness, sore throat, elevation in temperature, cyanosis, dyspnea	Fibrotic lesion in right apex	.....	Hodgkin's disease	.....	Sometime after the first roentgenogram of the chest was taken, another showed bilateral extensive infiltration Autopsy findings: A firm mass in R.L.L. with diffuse spread and nodulations in lung
72.*	Hochberg & Crastnopol	F 32	1 mo.	Pain in right arm and shoulder	Tumor mass in upper portion of right lung field	Extrinsic compression of R.U.L. bronchus and terminal part of right main bronchus	Fibrosarcoma	Exploration of chest	Tumor mass extended from right upper lobe into the lower lobe and chest wall, mediastinum and retrocardiac area
73.*		M 43	5 mo.	Pain in left side of chest, dyspnea, cough, hemoptysis, fatigue	Circumscribed mass in L.U.L.	.....	Fibrosarcoma	Left pneumonectomy	Patient died 24 days after operation of postoperative complications
74.*		F 44	3 mo.	Nonproductive cough, elevation in temperature, fatigue	Large tumor mass in posteromedial part, R.U.L.	.....	Lipomyxosarcoma	.....	Lung puncture performed; biopsy reported as lipomyxosarcoma; patient's condition too poor to permit surgery; she died several weeks after entering the hospital
75.*		F 52	4 mo.	Pruritus, generalized itch, pain in chest, headache	Opacity in the anterior part of the left chest in the region of the root of the lung	.....	Fibrosarcoma	Left pneumonectomy	Patient well 8 yr. after operation
76.*		M 61	1 mo.	Constipation, otherwise asymptomatic	Well-delineated opacity in the medial part of R.U.L.	Soft, smooth mass in R.U.L. bronchus; biopsy nonrevealing	Fibrosarcoma	Right pneumonectomy	Patient died 6 mo. after operation
77.*		F 62	2 yr.	Cough, pain in right side of chest	Opacity of the greater part of the right hemithorax	.....	Fibrosarcoma	Exploration of chest	Tumor was not resectable; Patient died 5 mo. after operation

* Previously unreported cases

Fibrosarcoma

The 27 patients having fibrosarcomas of the bronchopulmonary system constituted 35.1% of the 77 patients with primary sarcoma of that system. The ages of these patients varied from 9 to 66 years. Seven patients were below 30 and nine were above 56 years of age. Seventeen of the patients were males and ten were females.

The duration of symptoms before the patient came under medical care varied from four days to four years. Two patients were asymptomatic, eight had symptoms of less than four months' duration, and in five there were symptoms for more than two years. The symptoms in 25 patients were as follows: pain was encountered in 18 patients, 14 localizing it to the chest, 3 in the shoulder, and 1 in the arm; cough occurred in 16 patients; expectoration was noted in 12, in 7 of whom it was accompanied by hemoptysis; loss of weight occured in 7; dyspnea in 6; fever (more than 101 F) in 6; malaise in 5; wheezing in 3; weakness in 3; anorexia, chills, and edema of the ankles were each encountered in 2 patients, and the following symptoms were observed in single instances—night sweats, edema of the arm, vomiting, constipation, arthralgia, pruritus, generalized body itch, drooping of the eyelid, headache, and orthopnea.

In the 26 patients in whom information was given as to the location of the lesion, there was equal distribution between the two sides. On the left side there was one tumor in the main bronchus, six in the upper lobe, and another six in the lower lobe. On the right side there were two in the main bronchus, four in the upper lobe, six in the lower lobe, and in one patient the middle and lower lobes were involved.

The roentgenographic manifestations of this lesion were not distinctive. In some instances it consisted of a rounded, circumscribed, discrete mass within a lobe, whereas in others it was comprised of a diffuse opacity accompanied by a variable degree of atelectasis. Bronchoscopy is mentioned in 13 patients. A tumor was noted in eight patients, and in the other five there was no indication of a neoplasm. In some instances the tumor mass was described as a smooth, round, pale-pink, firm mass occluding the bronchial lumen, in other instances it was described as a soft polypoid mass, and in others it was described as a reddish-gray, sessile mass in the wall of the bronchus. A biopsy specimen was taken in seven cases. It was positive for fibrosarcoma in four cases, suggestive of a malignant lesion in two, and indicative of a benign lesion in one. In the case reported by Carswell and Kraeft (1950) bronchoscopic examination was negative on two occasions, but on repeat bronchoscopy several months later a round, smooth, nonulcerated, dark-red mass was noted in the lumen of the bronchus. A biopsy of this mass was reported as a fibrosarcoma.

Grossly, the bronchopulmonary fibrosarcoma arises from the wall of the bronchus and often has an endobronchial component as well as a parenchymal extension. The case reported by Black (1950) is representative of the majority of these cases. Most commonly, these tumors are fairly well delineated, firm, polypoid, white, yellowish, or pink masses of tissue. On cross section the color and consistency is not unlike that of the uncut surface of the tumor. These neoplasms vary in size from about 1.5 cm. in diameter to the one reported by Storey (1952) where the lesion occupied the lower three-fourths of the left hemithorax. Behrend and Kravitz (1951) and Iverson (1954) reported cases in which the neoplasm arose from the wall of a cyst in the lung.

The histopathologic appearances of these neoplasms do not differ in any way from the fibrosarcomas found in other parts of the body. In all recently reported cases the spindle cell, so characteristic of this lesion, shows frank criteria of malignancy. In accordance with Stout's concept, the use of the terms neurofibrosarcoma or neurogenic carcinoma have been omitted and all tumors composed of anaplastic fibroblasts

• Previously unreported cases

are regarded as fibrosarcomas. In only one of the recently reported cases was there any difficulty in differentiating between a fibrosarcoma and a leiomyosarcoma. In this case, reported by Storey, there was a suspicion that the tumor may have taken origin from the bronchial musculature.

Of the 27 cases, 19 received definite therapy. The other eight cases were either noted at necropsy or were irresectable at the time of surgical exploration. The duration of life after surgery, regardless of whether the patient had a lobectomy or a pneumonectomy, varied from 24 days to 8 years, the average life span after the operation being approximately 2 years. In two cases, postoperative x-ray therapy was given. In one of these cases, reported by Drewes and Willmann (1953), the patient was apparently well 20 months after the operation. In the other, reported by Iverson (1954), there was recurrence six months after the operation and fatal issue a year after the tumor was removed surgically.

In considering the duration of life of the patient with a bronchopulmonary fibrosarcoma, two cases are worthy of mention. The first is the one reported by Curry and Fuchs (1950). A 13-year-old girl expectorated a piece of tissue which on histologic examination was reported as a fibrosarcoma. Subsequent roentgenographic and bronchoscopic examinations over the next four years did not reveal recurrence of the tumor. The second case is the one reported by Verstraeten and Boels (1951). A 34-year-old woman was seen by a physician for the first time on March 3, 1947, because of pain in the left side of the chest and hemoptysis. A roentgenogram of the chest at this time disclosed a well-delineated tumor in the left upper lobe. Surgery was advised, but the patient refused. A roentgenographic examination of the chest on Sept. 12, 1948, disclosed considerable enlargement of the tumor. A study on Dec. 7, 1950, revealed still further increase in the size of the neoplasm. At this time the patient submitted to surgery, and a left pneumonectomy was performed. The tumor was reported as a primary "fusocellular sarcoma of the lung . . . resembling a neurofibrosarcoma." At the time of the report of this case (February 1, 1951) the patient was well.

A 43-year-old man, was admitted to the hospital on March 27, 1945, complaining of a sharp pain on the left side of the chest of about five months' duration. In recent weeks the pain had become rather severe. At the same time the patient noticed periodic dyspnea, a dry cough which was occasionally accompanied by the expectoration of bright-red blood, and extreme fatigue. About a year prior to the present hospital admission, the patient was operated upon for empyema of the left pleural cavity.

Examination at the time of the present admission revealed an acutely sick patient; the left side of the chest moved poorly with respiration. There were dullness to percussion over the upper third of the left hemithorax and diminished breath sounds in the left infraclavicular area. Hemograms, chemical studies of the blood, and urinalysis were within normal limits. Roentgenographic examination of the chest (Fig. 1), disclosed a circumscribed, globular mass in the posterior part of the left upper lobe.

On April 4, 1945, through a left thoracotomy, an extrapleural pneumonectomy was performed. The patient died on the 24th day postoperatively of a severe uncontrollable infection.

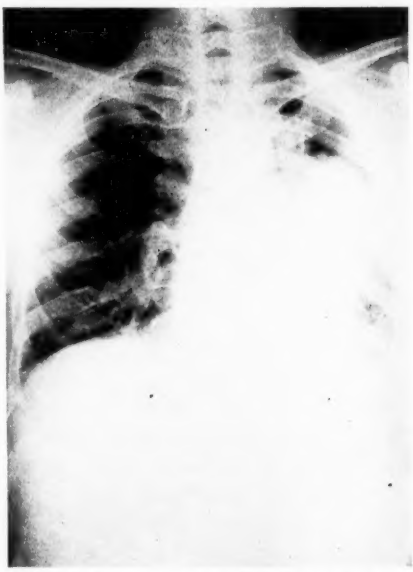

Fig. 1.—Roentgenogram of the chest discloses a large circumscribed opacity in the left hemithorax. (Same case as Fig. 2.)

The pathologist reported on the surgical specimen (Fig. 2) as follows: "The specimen consists of the left lung. The external surface, especially in the region of the upper lobe, is grey-violet, thick and glistening. On the posterior surface, in the region of the interlobar fissure, there is a firm mass palpable. On cross section of the lung a fairly well circumscribed tumor measuring 5×4 cm. is seen in the upper lobe and in the interlobar area of the lower lobe. The cut surface of the growth

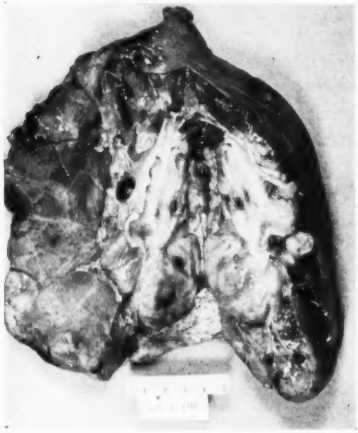

Fig. 2.—Sectioned left lung discloses a firm, circumscribed mass within the lung. (Same case as Fig. 1.)

is pink, tan, and gray. Its consistency is moderately firm. At 1.5 cm. from the origin of the left upper lobe bronchus there is a mass arising from its wall which extends distally. The tumor tissue in the bronchial wall does not involve the mucosa. Microscopy of the tumor revealed a variegated picture. The tumor is composed chiefly of spindle-shaped cells. In many of the cells the nuclei are vesicular and in other cells they are irregular and hyperchromatic. Some cells contain more than one nucleus. Mitotic figures are numerous. The tumor cells form intertwining bundles.

"Diagnosis—Fibrosarcoma of the lung."

A 62-year-old woman, entered the hospital on Sept. 21, 1948, complaining of an unremitting cough of two years' duration and pain in the right side of the chest and breast of three weeks' duration. She appeared both acutely and chronically ill. There was diminished expansion of the right side of the chest, dullness to percussion, and depression of the breath sounds over the greater part of the right hemithorax. Roentgenographic study of the chest (Fig. 3) revealed an opacity involving the greater part of the right side of the chest with some aeration of the upper part of the lung. The

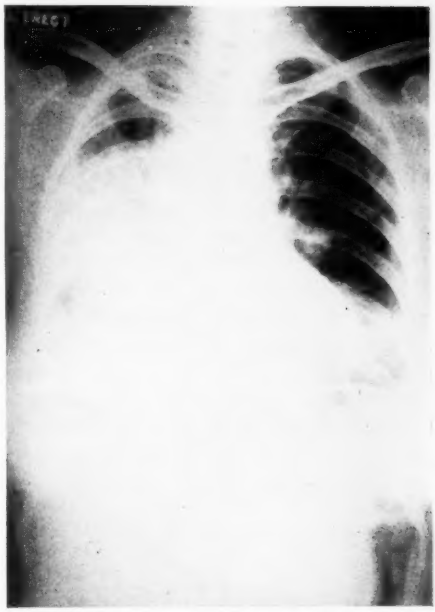

Fig. 3.—Opacity occupies most of the lower two-thirds of the right hemithorax.

mediastinum was not displaced. Hemograms, blood chemistry, and urine studies disclosed normal values.

On Sept. 29, 1948, the right side of the chest was explored. A diffuse, firm mass was palpated in the anterior midportion of the right lung. There were many large lymph nodes within the mediastinum, some discrete and others matted together. In view of these findings it was deemed inadvisable to remove the lung. Accordingly, some of the tissue was removed for biopsy purposes.

The pathologist reported on this tissue as follows: "Preparations from the tissues received show a variegated picture. In places the tumor cells are spindle-shaped and vary in size, shape and nuclear staining qualities. In other areas they are plumper but show similar variations in nuclear staining qualities. In some areas there are giant cells with more than one nucleus which show mitosis. The histopathologic picture is that of a fibrosarcoma."

Malignant Lymphoma

In 26 patients (33.8% of the total series of 77 cases) a diagnosis of malignant lymphoma of the bronchopulmonary system was made. Fourteen of these patients had lymphosarcoma, nine Hodgkin's disease, and three reticulum-cell sarcoma.

A. *Lymphosarcoma.* — Lymphosarcoma was present in 18.2% of the 77 patients with primary sarcoma of the bronchopulmonary system. The ages ranged from 34 to 70 years. The disease was equally divided between men and women.

Four of the 14 patients in this group were asymptomatic. Symptoms were present in the other ten patients from four weeks to seven years, five, or 56% of the cases, being ill four months or less before seeking medical care. Symptoms consisted of cough in seven patients, expectoration in six with hemoptysis in five; pain, five patients (three had it in the chest, one had it in the epigastrium, and one had it in the shoulder; loss of weight in four; dyspnea in three, and fever in another three. On one occasion each of the following was present: chills, swelling of the distal parts of the extremities, malaise, and weakness.

In eight patients the right lung and in six the left lung were the site of origin of the tumor. In two instances the right upper lobe was involved, in three the right lower lobe, in one the middle and lower, and in the other two the site of origin in the right lung was not mentioned. The lesion originated in the left upper lobe in three patients, the lower lobe in one, and in the other two the site of origin in the left lung was not given.

Roentgenographic appearances of a bronchopulmonary lymphosarcoma are not unlike those of a fibrosarcoma. The tumor mass may present as a discrete peripheral, central, or hilar opacity. At times the periphery of the tumor has a scalloped appearance. Hilar densities may be associated with strand-like infiltrations extending into the lung field. Occlusion of a bronchus will lead to signs of atelectasis of the lung distal to the obstruction.

Bronchoscopic examination was mentioned in only eight of the patients with bronchopulmonary lymphosarcoma. In none of these cases, except the one mentioned below, was an endobronchial lesion seen, although some narrowing of the bronchial lumen was occasionally noted. In the case reported by Grimes, Weirich, and Stephens (1954) an endobronchial neoplastic lesion was seen. Biopsy of this tumor revealed the presence of connective tissue infiltrated by leucocytes. Beck and Reganis (1951) mention another case, reported by Blades, in which tissue removed from the bronchus disclosed the presence of lymphosarcoma.

Grossly, these tumors are fairly firm in consistency, reddish-gray or pale-gray in color, and measure up to 8 cm. in diameter. Maier reported a patient in whom the entire left upper lobe was replaced by neoplastic tissue. On the cut surface they are usually fleshy, nodular and lobulated. At times the margins are fairly distinct, but frequently they are indefinite and infiltrate the neighboring pulmonary parenchyma and surround the bronchi in the form of a collar. Histologically, they consist of sheets and dense masses of closely packed, fairly uniform lymphoid cells with deeply staining nuclei. Mitotic figures are rather uncommon. Lymphoblasts invade and replace the parent tissue destroying its architectural pattern. Churchill reported a patient with a lymphosarcoma and coccidioidomycosis of the lung.

Of the 10 patients with bronchopulmonary lymphosarcoma submitted to surgery, one died 5 weeks and another 20 months after the operation. Six of the other eight patients were apparently well eight months to five years after surgery. In two patients no follow-up data were available. The two patients reported by Grimes, Weirich, and Stephens (1954) were alive and well two and five years after the operation. Maier's (1948) patient developed a recurrence in the right lung 19 months after pneumonectomy. Radiotherapy (1150 r to each of two fields) was given to the right side with almost complete disappearance of the lesion. The patient was apparently well 30 months after surgical intervention.

Report of a Case: The following case was reported previously by Spatt and Grayzel (1947).

A 34-year-old woman entered the hospital on Oct. 7, 1944, because of recurrent hemoptysis, cough, and pain in the chest for about three months.

The physical examination disclosed an area of impaired percussion below the right scapula and an occasional moist rale at the right base posteriorly. A roentgenographic study of the chest, disclosed an area of encapsulated fluid in the lower right hemithorax. Bronchoscopy revealed the presence of a purulent exudate in the right lower lobe bronchus. The patient was discharged from the hospital on Oct. 20, 1944, with a diagnosis of lung abscess.

She was treated at home with antibiotics but failed to improve and was readmitted to the hospital three months later. The physical findings in the chest were not remarkably different from those encountered at the time of the previous admission.

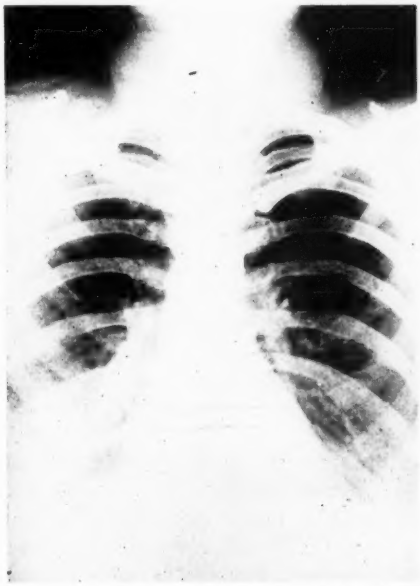

Fig. 4.—Opacity of the right lower lobe. (Same case as Fig. 5.)

However, roentgenographic studies of the chest disclosed an opacity at the right base posteriorly within which there was an area of necrosis (Fig. 4). On Jan. 26, 1945, the right lower lobe was removed. The pathologist reported on the tissue as follows:

The specimen (Fig. 5) consists of the right lower lobe of the lung. The external surface is purple-red and gray-pink with a reticular gray-white pattern. In the central portion an irregular, egg-shaped, moderately firm mass is palpable. On cut section one notes a good portion of the lung tissue to be replaced by moderately firm gray-white, gray-pink, and yellowish-gray tissue, measuring 7 cm. in its greatest diameter. The borders fade imperceptibly into the surrounding lung tissue. A bronchus measuring 0.9 cm. in diameter extends into the mass and is fused with it. As the bronchus enters the mass its lining mucosa assumes a nodular appearance. The lung tissue is pink-gray, and in places there are small bronchiectatic cavities. Microscopically, the striking picture is the collar of cells about the blood vessels. The tumor cells are large and round. Many are lymphoblasts and some show mitotic figures. In all preparations the cells about the lining bronchial epithelium merge with the sheets of cells forming the collar about them. The tumor cells are also seen in places extending along the septa into the deeper portions. Diagnosis—right lower lobe of the lung with lymphoblastoma (lymphosarcoma).

Fig. 5.—Resected right lower lobe cut across to show the infiltrated, dense tumor. (Same case as Fig 4.)

B. *Hodgkin's Disease.* — Nine patients (11.7% of the 77 cases under consideration) had primary bronchopulmonary Hodgkin's disease. The ages of these patients ranged from 18 to 65 years with seven, or 78% being 30 years or less. Five of the patients were women and four were men.

In six of the eight patients in whom the duration of symptoms is mentioned, it varied from one week to 18 months, and in five of these it was less than 4 months. The other two patients were asymptomatic. The patient reported by Heatley (1950) was known to have had a pulmonary lesion two years previous to coming under the care of the surgeon. The patient reported by Efskind and Wexels (1952) was similarly known to have had a pulmonary lesion for

two years before it was shown to be Hodgkin's disease. The symptoms encountered in the patients with primary bronchopulmonary Hodgin's disease were cough, dyspnea, and fever in each of five patients; expectoration in three, with hemoptysis in one of these patients, and malaise, loss of weight, and pain in each of two patients. On one occasion each of the following was encountered —cyanosis, irritability, night sweats, sore throat, vomiting, and weakness.

The right upper and lower lobes were involved in each of two patients. In another two patients the site in the right lung was not recorded. The left upper lobe was involved in one patient, and in two others the location in the left lung was not specified.

The roentgenographic features of bronchopulmonary Hodgkin's disease are similar to those of other forms of primary sarcoma of the lung and/or bronchus. Typically, the roentgenographic lesion in Hodkgin's disease consists of an infiltration of the lung or a mass within the substance of the lung. Where the mass is located in the hilar part of the lung, distal atelectasis may be present. Ipsilateral pleural effusion is relatively commoner in this type of primary bronchopulmonary sarcoma than in the other forms of these tumors. Efskind and Wexels (1952) reported two cases of primary pulmonary Hodgkin's disease in whom the tumor had undergone necrosis and cavitation. The roentgenograms in these two patients disclosed irregular cavities surrounded by dense and irregular infiltration of the lung.

Bronchoscopy was performed in six of the nine patients with primary bronchopulmonary Hodgkin's disease. It was essentially negative in three cases. In the other three patients a smooth red or granulomatous tumor was seen which encroached upon the bronchial lumen. In the case reported by Heatley (1950) biopsy of the lesion was reported as lymphoma, possibly Hodgkin's disease. In the case reported by Higginson and Grismer (1950) the biopsy was reported as a squamous-cell carcinoma. However, biopsy on another occasion was reported as Hodgkin's disease with squamous metaplasia of the bronchial mucosa. In the third case, reported by Soulas (1945), the biopsy was reported as lymphogranulomatosis. Bronchoscopic biopsy at a later date was reported as Hodgkin's disease.

Grossly, these tumors are infiltrative growths, pink-grey in color irregular and/or nodular on the surface, and not infrequently forming a collar about the bronchus. They infiltrate the surrounding lung tissue and are therefore poorly delineated from the pulmonary parenchyma. The cut surface of the tumor discloses a more or less homogeneous consistency. In the two cases reported by Efskind and Wexels (1952) cavitation was present. Histologically, there is atypical lymphoid hyperplasia and a heterogenous collection of cells interspersed between eosinophiles and giant cells of the Reed-Sternberg variety. The pathognomonic cell in these tumors is a large reticular cell with abundant cytoplasm, a large round nucleus, and a prominent nucleolus. These cellular elements are embedded in fibrous tissue which often separates the cellular elements into nests. D'Amato, Latienda, and Pizarro (1947) reported a patient in whom Hodgkin's disease and active pulmonary tuberculosis coexisted in the same part of the lung.

Of the six patients who received therapy, two were subjected to simple exploratory thoractomy, two received x-ray therapy, and the other two had pulmonary resection. One of the patients who had excisional surgery also received postoperative x-ray therapy. This patient died two years after surgical intervention. One patient who received radiotherapy alone was alive and well six months after the therapy was instituted.

C. *Reticulum-Cell Sarcoma.*—There were 3 patients, or 3.9% of the 77 patients, in whom the histopathologic diagnosis was reticulum-cell sarcoma. All three were males. Their ages were 3½, 15, and 37 years. The duration of illness in these patients was respectively three years, six months, and five months. The symptoms encountered were dyspnea in all three, cough in two, pain in the chest in another two, and pain

in the arm in one. Fever, anorexia, hemoptysis, night sweats, loss of weight, malaise, and pulmonary congestion were each encountered on one occasion. In all three patients the right upper lobe was the site of origin of the neoplasm.

Roentgenographic studies of the chest in all three patients showed a cyst or cyst-like mass in the involved area. In the case reported by Ransdell, Bailey, and Ellison (1951) they remark that, "a routine Public Health 70 mm. survey chest film taken at the patient's place of employment November 26, 1950, followed by a 14×7 film November 29, revealed a small ill-defined mass projecting from the right upper mediastinum at the level of the first interspace anteriorly and a cystic appearance of the right upper lung field. [A roentgenogram of the chest taken when the patient entered the University Hospital in February, 1951] revealed marked enlargement of the previously noted hilar mass and the development of a fluid level in the cystic area." Bronchoscopy was performed in only the latter case. The bronchial tree in this patient was essentially normal. Bronchial washings did not disclose any cells which would contribute to a definitive diagnosis.

The gross and microscopic appearances of a reticulum-cell sarcoma are best described in the word of Ransdell, Bailey, and Ellison (1951), who describe their cases as follows: "The gross specimen consists of the upper lobe of the right lung. There is a loculated cyst 7 cm. in diameter which replaces the apical portion of the lobe and which is filled with serosanguinous fluid. . . . The wall of the cyst consists of moderately heavy fibrous connective tissue. Inferiorly and in part medially to the cyst is a necrotic tumor mass 7×6 cm. which extends to the medical line of excision [of the lobe]. . . . The center of the approximately spherical neoplastic mass lies well within the lung and invades the fibrous wall of the cyst at its medial inferior portion. . . . Only a narrow shell of the neoplasm remains viable around the periphery of the necrotic tissue. . . . The cells of the viable neoplasm suggest origin from the septal reticulum. The cells are large, generally with solitary nuclei, but occasionally binucleated and multinucleated; there is pleomorphism as well as anisocytosis and anisokaryosis. The nuclei are vesicular and hyperchromatic with prominent chromatin which is at times arranged primarily circumnuclearly; there are prominent nucleoli. While there are anastomotic processes between cells, there is also deposition of the reticulum. The neoplastic cells form the support for thin-walled capillaries. . . . There is a striking resemblance between the tumor cells and the macrophages in the subjacent pneumonitis which, with the exception of nuclear anaplasia, is most striking." Although the tumor in this case arises from a cyst wall it is not necessarily so in other cases.

The only patient in this group subjected to definitive treatment was the one reported by Ransdell, Bailey, and Ellison. Here, a right upper lobectomy was performed following x-ray therapy, a tumor dose of 4500 r being given. The patient was apparently well three months after the operation.

Leiomyosarcoma

There were 13 patients in the collected series of cases (16.9%) in whom the diagnosis of pulmonary leiomyosarcoma was made. In this group of cases there were four males and nine females. The ages ranged from 6 to 67 years. Three patients were in the first decade of life, one was 34 years of age, three were between 52 and 57, and six were between 63 and 67 years of age.

In nine patients in whom the duration of illness is mentioned, it varied from two weeks to two and a half years. In four of these patients it was four months or less. Cough was present in 10 patients; pain in 8 (seven had pain in the chest, and one had pain in the substernal area); dyspnea in 7; expectoration in 5, with hemoptysis in 2; loss of weight and fever in 3; and weakness and/or malaise in 3. Anorexia, constipation, listlessness, orthopnea, and pal-

pitation occurred in single patients.

The right lung was the site of origin in seven cases and the left in six. The lesion was confined to the right upper lobe in one patient and to the lower lobe in another case. In two other instances it involved the right middle and lower lobes. In the other three patients it arose from the right main bronchus. On the left side the site of origin was the upper lobe in two and the lower lobe in another two patients. In one patient it arose from the left main bronchus and in another the site of origin in the left lung was not specified.

Roentgenographic studies of the chest in the patients with leiomyosarcoma of the bronchopulmonary system oftenest disclosed a solitary, circumscribed density with minimal infiltration of the lung about this opacity. In one of the patients reported by Watson and Anylan (1954) there was cyst-like formation in the region of the neoplasm. In those instances in which the neoplasm produced bronchial obstruction, atelectasis was also present.

Bronchoscopy was performed in 10 patients. The most frequent finding was a dark-red, smooth, fairly firm endobronchial mass. In one instance, some blood was seen in the bronchial lumen. Bronchoscopy was essentially negative in three patients; in five the biopsy was positive for leiomyosarcoma, and in two the biopsy was negative. Aspiration and/or bronchial lavage in three patients yielded cells which were atypical in one and negative for tumor cells in the other two patients.

Johnson, Mangiardi, and Jacobs (1952) reported an endobronchial leiomyosarcoma which measured 1.2 by 1.7 cm. The tumor infiltrated the bronchial wall, but the pulmonary parenchyma in juxtaposition to the tumor was not involved. In one of the cases reported by Watson and Anylan the tumor was 5 cm. long and within the wall of the main bronchus. Here, too, the lung in proximity to the neoplasm was free of tumor tissue. In another case reported by these authors, the tumor was well encapsulated and attached to the lung but did not invade the pulmonary substance. Killingsworth and his associates (1953) reported an endobronchial leiomyosarcoma which extended beyond the bronchial wall, through the pulmonary vein, and into the left atrium.

The leiomyosarcoma of the bronchopulmonary system is of variable color—often gray, blue, and dark-red, soft, and even cystic in consistency. It is often well delimited from the surrounding lung tissue. Histologically, the tumor is composed of bundles of spindle-shaped and ovoid cells arranged in a fascicular pattern. Judging from the histologic appearance of these tumors they are of low-grade malignancy.

Definitive surgical therapy was undertaken in 7 of the 13 patients. Two of these patients had complete removal of the involved lung (one of these patients was well two years after the operation); one patient was subjected to a first-stage pneumonectomy but died soon thereafter; two patients had the right middle and lower lobes removed (one was well four months and the other six years after the operation); and two had local excision of the tumor (one of these patients was well five years after the operation). Of the other six patients exploratory thoractomy was performed in two, x-ray therapy was started in another but had to be abandoned because of the patient's poor condition, and the other three patients received only symptomatic care.

Carcinosarcoma

There were five patients (6.7% of the total series of sarcomas) in whom the diagnosis was primary carcinosarcoma of the bronchopulmonary system. The ages of these patients were 51, 55, 56, 57, and 69 years. Four of the patients were men. The duration of illness varied from six weeks to a year, four of the patients being symptomatic for four months or less before seeking medical attention. The symptoms encountered in the patients with carcinosarcoma were cough, expectoration, fever, loss of weight, malaise, and pain in each of three patients. (In one patient the expectorated mucus contained blood.) The only other

symptom encountered was dyspnea in one patient.

In three patients the disease began in the right lung and in the other two in the left lung. The sites of origin were the right upper lobe in two, the right main bronchus in one, the left upper lobe in one, and the left main bronchus in the other patient.

Roentgenographic manifestations were protean and resembled other neoplasms in the same location. In one case a hilar mass was seen with retrograde extensions from it into the right upper lobe; in another patient there was a well-circumscribed mass within the substance of the right upper lobe, and in the other cases there was bronchial obstruction with lobar, bilobar, and pneumonic atelectasis. Bronchoscopic examination was performed in four of the five patients, and a mass was noted in three. The tumor was described as a papillary growth in one case, as necrotic in another, and simply as a mass in the third case. In the fourth case the bronchoscopist described his findings as "intrabronchial granulations." Tissue removed for biopsy via the bronchoscope in three patients was reported as nonmalignant in two instances and as unclassified malignancy in the third. In the latter patient two previous bronchoscopic biopsies had been reported as negative for tumor tissue.

Grossly, these tumors showed several similarities. All had an endobronchial component with an extrabronchial extension of the lesion into the pulmonary parenchyma. In the cases reported by Bergmann and coworkers (1951) and by Taylor and Rae (1952) the tumor was relatively small, being six centimeters in its largest diameter. In the case reported by Hochberg and associates the tumor measures 11.5 by 10 by 5 cm. In one of the cases reported by Taylor and Rae the tumor was attached to the bronchial wall by a small, short pedicle. On cut section the tumor varied in color from yellowish-pink to tan-gray. Areas of bleeding into the tumor mass were occasionally present. The consistency of the tumor both on its cut surface and exterior was of a rubbery nature. Histologically, the cases reviewed consisted of epidermoid carcinomatous elements and fibrosarcomatous tissue. Bergmann, Ackerman, and Kemler (1951) reviewed nine cases of primary carcinosarcoma of the lung and found that most of the cases were of similar histopathology.

Surgical removal of the lesion was applied in four of the five patients. One of the patients died soon after the operation. The other three were apparently well 18 months, 3, and 6 years after the operation.

The following case was previously reported by Hochberg, Grayzel, Berson, and Rosenberg (1949).

A 55-year-old woman entered the hospital on Aug. 9, 1947, complaining of a chronic cough of 10 years' duration which had become very distressing in recent months. About the same time the patient observed streaks of blood in the sputum. Except for some dullness to percussion over the upper medial third of the left side of the chest posteriorly, the physical examination was essentially negative. The hemograms, blood chemistry, and urine were not remarkable. Roentgenographic examination of the chest (Fig. 6) disclosed a well-circumscribed mass in the posteromedial part of the left upper lobe.

On Aug. 22, 1947, the chest was explored. A

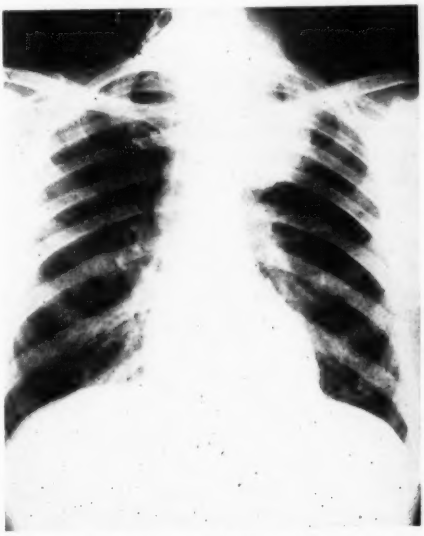

Fig. 6.—There is a well-delineated opacity in the upper medial part of the left upper lobe. (Same case as Fig. 7.)

large circumscribed mass was found within the substance of the medial part of the left upper lobe of the lung. There was no evidence of metastasis to the mediastinum, and, therefore, the left upper lobe was removed. The patient failed to recover after the operation and died 17 hours after the conclusion of the operation. The surgical specimen (Fig. 7) was described by the pathologist as follows:

The surgical specimen consisted of the upper lobe of the left lung. It was pinkish-gray, soft, and noncrepitant. Projecting above the surface and within the substance of the lung there was a firm, pinkish-yellow, irregular mass, 11.5 by 10 by 5 cm., which was sharply demarcated from the adjacent lung tissue. The cut surface of the mass

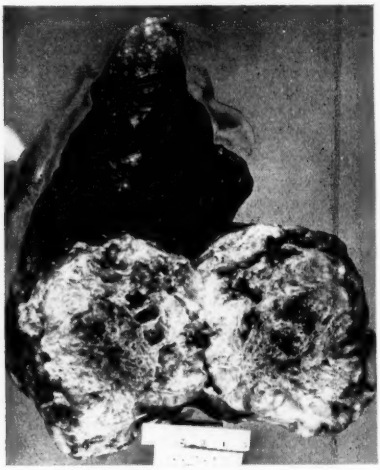

Fig. 7.—Sectioned left upper lobe demonstrates the tumor. (Same case as Fig 6.)

was uniformly soft and yellowish pink. The center of the neoplasm was hemorrhagic. Microscopy of the mass showed a varied picture. The cells were spindle-shaped, varying in size, with ovoid or round vesicular nuclei. Some of the cells were hyperchromatic and the occasional cell showed mitotic division. The cells were arranged in intertwining bands or in whorls. Intermingled with these cells there were nests of large ovoid cells of varying size and shape. Diagnosis—Fibrosarcoma and epidermoid carcinoma.

Miscellaneous

In this group of cases there were two patients with lipomyxosarcomas, two with chondrosarcomas, one who had an angiosarcoma and another with a malignant giant-cell sarcoma of the lung. The sex distribution of these cases was four men and two women. The ages of these patients were given in five subjects as 41, 43, 44, 47, and 57 years. The duration of illness before these patients sought medical care was 2 to 18 months; half of the patients were ill 3 months or less before they were seen by a physician. The symptoms in these patients were cough in four, pain in four (the pain being in the chest in three and in the arm and shoulder in one), dyspnea and fever present in three, and loss of weight and fatigue present in two. Expectoration, dysphagia, dysphonia, anorexia, ankle edema, articular pains, tachycardia, and palpitation were each present in single instances. The right upper lobe was the site of origin in three patients and the upper and middle lobes in another case. On the left side the neoplasm arose from the left main bronchus in one case and the lower lobe in another.

Roentgenograms of the bronchopulmonary system were protean, varying from that of a localized mass in the substance of the lung to a massive atelectasis of one lung.

Bronchoscopic examination performed in three patients failed to reveal an endobronchial lesion. In one patient extrinsic pressure upon the bronchus was noted, suggesting the presence of an extrabronchial tumor. The bronchial aspirate, studied in one patient, did not disclose the presence of neoplastic cells. In one case the diagnosis of lipomyxosarcoma was made on the tissue obtained via lung puncture. The diagnosis in four patients was made on the tissue obtained at necropsy and in another on the tissue obtained at the time of exploration of the chest. Definitive surgical care was not applied in any of the patients in this group of cases.

A 44-year-old woman entered the hospital on April 3, 1945, acutely ill and complaining of a nonproductive cough of three months' duration, a low-grade fever, and extreme fatigue. The only positive findings on physical examination were suppression of the breath sounds and an occasional moist rale in the right parascapular area. Roentgenographic examination of the chest disclosed a large tumor mass of uniform density in the posteromedial part of the right upper lobe. The blood and urine studies did not disclose any deviations from the normal.

The patient's general condition was too poor to permit exploratory thoracotomy. Accordingly, a lung puncture was performed on April 4, 1945. The tissue thus obtained consisted of loosely arranged connective tissue composed of numerous spindle-shaped and stellate cells. There were also present many large mononuclear cells and some multinucleated cells with irregular hyperchromatic nuclei. Dispersed between these cells were nests of adipose tissue cells. Diagnosis—Lipomyxosarcoma.

Comment

In the present series of 77 cases there were 45 male subjects and 32 females, a sex ratio of 1.4:1. The ages of the patients ranged from 3½ years to 70 with the arithmetical mean age at 43 years. Giraud, Bernard, Metras, and Orsini (1947) reported a three and a half-year-old child with a primary reticulum-cell sarcoma of the right upper lobe. Watson and Anlyan (1954) reported a four-year-old boy with a leiomyosarcoma of the right main bronchus. Sherman and Malone (1950) had under their care a six-year-old girl who had a myosarcoma of the right main bronchus. Killingsworth, McReynolds, and Harrison (1953) reported a seven-year-old girl with a similar tumor in the left main bronchus. The oldest patient was a 70-year-old man with a lymphosarcoma of the left upper lobe, reported by Sarokhan and Morrison (1953). Only 18, or 23.4% of the cases, were less than 30 years of age, whereas 32, or 41.6%, were more than 51 years of age. This is contrary to the view of many writers that primary sarcoma of the bronchopulmonary system is a disease of the younger age group. The age-sex distribution of the 77 cases is as follows:

Age, Years	Male	Female	Total
Up to 10	3	2	5
11-20	3	1	4
21-30	5	4	9
31-40	10	3	13
41-50	6	8	14
51-60	11	3	14
61-70	6	11	17
Not given	1		1
Total	45	32	77

The duration of illness before the patient came under the care of a physician was variable. Eight, or 10.4% of the seventy-seven cases, were asymptomatic. Of the remainder, symptoms were less than four months in duration in 30, or 43.5% of the cases. Of the eight patients with primary bronchopulmonary Hodgkin's disease in whom symptoms were manifest, six, or 75%, were of less than four months' duration. Four of the five patients with carcinosarcoma were ill less than four months before seeking medical care.

The incidence of the cardinal symptoms in the 69 patients with primary bronchopulmonary sarcoma who mentioned symptoms are cough in 48, or 69.6% of the cases; pain in 43 patients, or 62.3% of the 69 cases, with 34, or 49.3% of the total series having thoracic pain. Expectoration was present in 31, or in 44.9% of the patients, with hemoptysis in 17, or 24.6% of the cases. Dyspnea was present in 28 patients, or in 40.6% of the cases; fever in 24 patients, or 34.8%, and loss of weight in 22, or 31.9% of the 69 patients. This train of symptoms is not unlike that encountered in patients with other types of lung tumors. Symptoms, as in other lung tumors, are dependent upon the location of the neoplasm, its manner of growth, and the nature of its interference with function of the surrounding tissues.

Tumors beginning in the proximal portion of the bronchial tree and growing into the lumen of the bronchus often initiate cough and expectoration with or without hemoptysis. Those in the periphery of the lung may lead to a sense of discomfort or pain in the area corresponding to the location of the tumor. Pain may also be due to pleural involvement and/or impingement upon anatomically related tissues. Those neoplasms beginning in the intermediary area remain relatively asymptomatic until they have attained sufficient size to impair respiratory function, or have metastasized. Tumors arising in the hilar region, without invading the bronchial lumen or causing secondary changes in the bronchial wall,

may also remain asymptomatic until such time as they produce sufficient extrinsic pressure upon the bronchus to cause obstruction. The subsequent train of symptoms will depend upon the manner of growth of the tumor and the accompanying pulmonary and vascular changes—atelectasis, necrobiosis of the tumor, inflammatory changes in the lung, and interference with cardiovascular function. Tumors invading the pulmonary vascular bed may cause chronic, subacute, or acute cor pulmonale. In the case reported by Lowell and Tuhy (1949), a tumor mass extended into the right pulmonary artery to within a centimeter of the pulmonary valve. Durgin and Ingleby (1946) reported the case of a 53-year-old woman with a primary sarcoma of the pulmonary artery. The patient died 12 hours after entering the hospital. Autopsy disclosed that the site of origin of the tumor (a fibrosarcoma) was just above the beginning of the pulmonary artery. In reviewing the subject of sarcoma of the pulmonary artery, these authors found four similar cases reported in the literature. The common clinical manifestation of this lesion is right ventricular hypertrophy and dilation with signs of cor pulmonale.

Conventional roentgenograms of the chest of the patient with a primary sarcoma of the bronchopulmonary system may disclose involvement of any and all parts of the lung. Not uncommonly, the pulmonary lesion is a solitary, circumscribed, fairly homogeneous density. More commonly, this lesion is lobar rather than pneumonic. Irregular infiltrating strands may extend from the opacity peripherally into the pulmonary parenchyma. In other instances, particularly in the lymphomatous group of cases, the periphery of the tumor opacity has a scalloped appearance. Necrosis of the neoplasm is evinced by a fluid level or irregular translucency within a thick-walled cavitary lesion. Two such cases were reported by Efskind and Wexels (1952). In other instances the lesion consists of a unilateral hilar infiltration extending in linear fashion into the pulmonary parenchyma distal to the parent lesion. When the lesion occludes the bronchial lumen, atelectasis ensues and roentgenograms of the chest at this stage will disclose characteristic signs. Not uncommonly, fluid may be noted in the ipsilateral pleural cavity. At times the effusion may reach such volume as to displace the mediastinum to the contralateral side. Widening of the mediastinum is usually an indication of extension of the disease to that area.

Many coexisting and unrelated conditions have been reported in patients with proved primary bronchopulmonary sarcoma, i.e., pleural thickening, pulmonary emphysema, pulmonary fibrosis, pulmonary tuberculosis, and silicotuberculosis, as well as cysts of the lung. In three instances the neoplasms were found to arise from the wall of a cyst. Behrend and Kravitz (1951) reported a fibrosarcoma arising from the wall of a cyst within the right lower lobe; Giraud, Bernard, Metras, and Orsini (1947) reported the case of a reticulum-cell sarcoma which originated from the wall of a cyst of the right upper lobe; Ransdell, Bailey, and Ellison (1951) reported a similar case which also arose in the right upper lobe.

Bronchographic and tomographic studies of the lung may help locate the lesion, but they do not add anything which would help one make a specific histopathologic diagnosis.

Bronchoscopy was performed in 45 of the 77 patients. It was nonrevealing in 21 patients, and in the other 24 there were indications of bronchopulmonary pathology. In these cases the bronchoscopist often described the presence of a yellowish, red, or brown smooth mass projecting into the lumen of the bronchus or a more or less uniform narrowing of the bronchial lumen. In other instances granulation tissue was seen on the bronchial wall or ulceration of the mucosal surface of the tumor. In the occasional instance blood was noted within the lumen of the bronchus. The neoplasm proper was of variable consistency, sometimes rather firm and in other instances fairly soft and friable. Tissue for biopsy

purposes was removed from the tumor in 21 patients. The tissue was representative of the tumor in eight patients, or in 38.2% of the biopsies; suggestive of neoplastic disease in three patients, or in 14.3% of the biopsies and essentially negative for neoplastic cells in the other 10 patients, or in 47.6% of the biopsies. These statistics are based upon the observations and biopsy studies made at the time of the first or single bronchoscopic examination. Some of the patients had several studies before a positive histopathologic diagnosis was made on the tissue removed via the bronchoscope. A case in point is the one reported by Bergmann, Ackerman, and Kemler, i.e., Case 9 in the Table. Bronchial aspiration via the bronchoscope was performed in six cases. Atypical cells were present in but one case, i.e., Case 66 of the Table, reported by Watson and Anlyan.

Some doubt may exist in the mind of the reader as to whether or not primary pulmonary Hodgkin's disease should be included in the category of a primary sarcoma of the bronchopulmonary system. The generally accepted view that this disease is a special form of malignant lymphoma justifies its inclusion here. Regarding Hodgkin's disease, Scott (1948) states, "it is a reticulosis in which the proliferative reticulum becomes differentiated into collagen fibrils and myeloid cells. It differs from many other diseases in this group [of reticuloses] by starting as a local affection of lymph nodes and becoming generalized only in the later stages."

Carcinosarcoma implies the commingling of tumor elements which are both carcinomatous and sarcomatous, arising at the same site from epithelial and mesenchymal elements. Willis believes that the carcinosarcoma is a pleomorphic variant of an anaplastic carcinoma in which the more immature elements simulate sarcomas. Bergmann, Ackerman, and Kemler (1951) reviewed the cases of primary carcinosarcoma of the lung published prior to the latter part of 1951. They collected eight cases from the literature and added two seen at Barnes Hospital. In this series they included a case reported by one of us (L.A. H.) as a fibrosarcoma with coexisting carcinoma of the lung. We believe that Bergmann, Ackerman, and Kemler are justified in concluding that this case is one of carcinosarcoma, since there is commingling of the two neoplastic elements and no evidence that either of these tumors began in any area other than the same site in the lung. The simple commingling of the neoplastic elements is not prima facie evidence of the presence of a carcinosarcoma, for the tissue examined may represent a chance collision site of two independent tumors of the lung. Another possibility, although more remote, is metastasis from an extrapulmonary sarcoma or carcinoma to a primary carcinoma or sarcoma of the lung. Rabson, Stier, Baumgartner, and Rosenbaum (1954) reported the case of an adenocarcinoma of the cecum which metastasized into a sarcomatous area in the lung.

The treatment of primary sarcoma of the bronchopulmonary system is the same as that of any other malignant tumor, namely, removal. At the present time there are three modalities which may be applied: (1) x-ray therapy, (2) excisional surgery, and (3) a combination of x-ray therapy and excision. There are too few cases to permit definitive conclusions as to the relative merits of these procedures. The obvious impression one gains from the data presented in the foregoing is that early care is oftener followed by better results than are those cases where there is considerable delay in instituting definitive treatment. It is manifestly unfair to conclude, from the data presented, that x-ray therapy has little or no merit. The patients submitted to x-ray were apparently advanced cases and therefore do not form a suitable basis upon which to assess the merits of this form of therapy. However, it is our impression that this form of therapy is no better in primary bronchopulmonary sarcoma than it is in carcinomas of the same organ, and, therefore, "it is an unwarranted risk in any patient in whom treatment by resection

is not contraindicated." The efficacy of x-ray therapy in lymphomas, however, is well established.

Summary and Conclusions

A review of 77 cases of primary bronchopulmonary sarcoma is presented. This includes six of our own cases previously unreported.

The disease has no age limits, occurring in the very young as well as in older subjects, 41.6% of the cases occurring in patients more than 51 years of age.

Approximately 10% of the cases were asymptomatic. Symptoms are more frequently dependent upon the location of the tumor rather than upon its morphology. The duration or character of symptoms is no criterion upon which to base a diagnosis or prognosis even with the most definitive care.

The diagnosis of this condition is histopathological rather than clinical. The experiences with this relatively small number of cases precludes the formulation of any opinion as to prognosis.

In all suspected cases the patient should be given the benefit of doubt and submitted to surgery, unless there are specific contraindications to so doing.

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Sodium Amidotrizoate (Hypaque) and Sodium Acetrizoate (Urokon)

Comparison of Efficacy in Intravenous Urography

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In order to evaluate the efficacy of sodium amidotrizoate (Hypaque) 50% as a medium for use in intravenous urography, a group of 109 patients was studied.

The pharmacologic aspects of sodium amidotrizoate are described adequately in literature available from the manufacturer and will not be given here.*

In 109 consecutive patients referred to the Radiology Department of the University of California Hospital for intravenous urographic studies, sodium amidotrizoate 50% was used as the opaque medium. Blood pressure determinations were done before the examination was started. Approximately one-half of the patients then received intravenous injections of 30 cc. of sodium amidotrizoate. For the other half of the group, the amount of medium was modified according to total body weight, i.e., those patients weighing 100 lb. (45 kg.) or less received 20 cc.; 100 to 150 lb. (45 to 68 kg.), 30 cc., and more than 150 lb. (68 kg.), 40 cc. No advantage accrued from adjusting the amount to the body weight, and this has been abandoned.

Films were then taken at 5-, 10-, and 20-minute intervals after injection. At the time the 20-minute film was taken, another blood pressure determination was made. Also at this time any systemic or local side-effects were recorded.

In another group of 114 consecutive patients referred for intravenous urographic studies, sodium acetrizoate (Urokon) 50% was used as the medium. The method of examination was identical with that already described with the same film study, blood pressure determinations being done. The side-effects were recorded. A comparison was made between the incidence and type of reactions in this group of patients and those in patients for whom sodium amidotrizoate 50% was used.

Two years earlier a similar study had been conducted on a group of 54 patients with use of sodium acetrizoate 30% as the medium of choice. No blood pressure determinations had been made in this group of patients. The films of the patients in whom sodium acetrizoate 30% had been used were collected and mixed at random with the films of the patients in whom sodium amidotrizoate 50% had been used. The films were viewed simultaneously but independently by two viewers who had no indication as to which of the media had been used. The following were evaluated and graded:

Nephrogram (yes or no)
Time of maximum concentration (5, 10, or 20 minutes)
Concentration of the medium within the tubules (yes or no)
Caliceal size (Grades 1-4)
Caliceal extent (whether it was believed that on any one film all the expected caliceal groups were demonstrated, Grades 1-4)
Caliceal density (Grades 1-4)
Pelvic size (Grades 1-4)
Pelvic density (Grades 1-4)
Ureteral visualization (percentage)

In this study, Grade 1 corresponds to "poor," and Grade 4 to "excellent." In grading caliceal size and pelvic size, a structure consisting of a fine line of opaque medium was considered as Grade 1. If, however, the structure appeared in its expected anatomic form without evidence of dilatation, it was considered as Grade 4. Tubular opacification was recorded if one of two types was present; the first type was opacification of the renal papillae, which is actually part of the nephrogram density. The second type consisted of opaque striations radiating from the calices and representing sufficient concentration in the distal tubules to allow for demonstration.

The percentage of ureteral visualization was computed by using the film which, in each patient's series, showed the greatest degree of ureteral opacification. An assessment was made of the total extent of ureteral demonstration combining both

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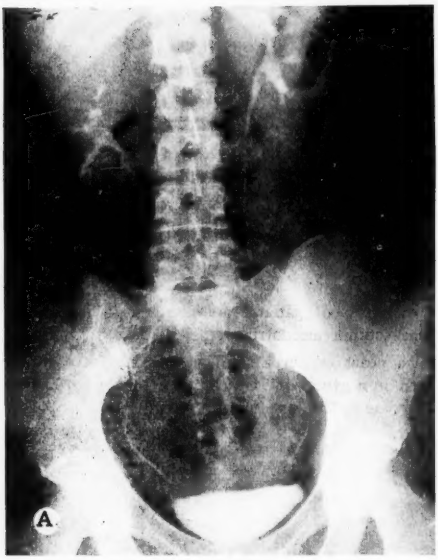
* References 1 and 2.



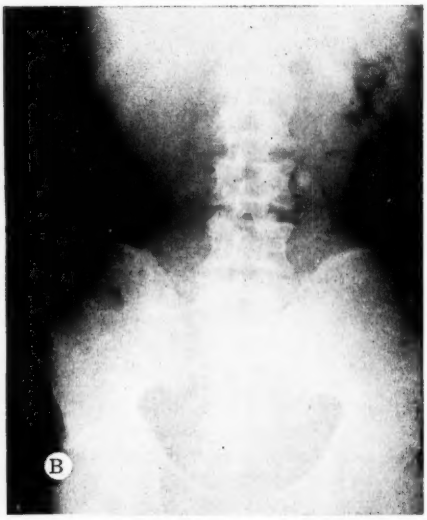


Fig. 1.—Illustrative films of an excellent (*A*) and a poor (*B*) urographic study. The gradings were as follows:

	A	*B*
Caliceal size	3	1
Caliceal extent	4	1
Caliceal density	4	1
Pelvic size	3	1
Pelvic density	4	1
Ureteral visualization	95%	5%

sides. This total was divided by two to obtain the average extent of ureteral visualization. For example, if one ureter was demonstrated in its entirety, representing 100%, and the other was shown to only 50% of its extent, the total grade would be 150%; this total divided by two would give an adequacy of 75% for total ureteral visualization. An example of an excellent urogram and grading is shown in Figure 1*A* and a poor urogram in Figure 1*B*.

The results of all such determinations were tabulated and compared. In those cases where a gross disease process which would tend to produce hydronephrosis was present, film grading was not attempted, and those patients were included in the reaction studies only.

Results

Reactions.—In 31% of the patients receiving sodium amidotrizoate as the injected medium some form of reaction was recorded. With 50% sodium acetrizoate, 34.3% of the patients experienced reactions. The type of incidence of such reactions are listed in the Table. Sodium amidotrizoate was distinctly superior in its lower incidence of all forms of reactions except arm pain. Nausea and vomiting produced the greatest discomfort to the patient and were considered severe reactions. Sodium amidotrizoate showed a marked advantage in this respect.

Summary of Reactions to Sodium Acetrizoate 50% and Sodium Amidotrizoate 50%

	Sodium Acetrizoate 50%		Sodium Amidotrizoate 50%	
	No. of Patients	% of Total	No. of Patients	% of Total
Nausea	8	7.0	8	7.3
Nausea and vomiting	5	4.4	2	1.8
Nausea, vomiting, and faintness	6	5.3	2	1.8
Nausea and faintness	7	6.1	6	5.5
Faintness	7	6.1	5	4.6
Pain	2	1.8	8	7.3
Flushing	--	----	1	0.9
Itching	--	----	1	0.9
Urticaria	1	0.9	1	0.9
Nausea, vomiting, and urticaria	1	0.9	--	----
Others	2	1.8	--	----
No reaction	75	65.7	75	68.8
Total	114	100	109	100

Blood Pressure Changes.—An arbitrary range of a normotensive response was set as plus or minus 5 mm. Hg systolic pressure above or below the blood pressure recorded

at the start of the examination. The patients recording a drop of 6 mm. Hg or more were reported as showing a hypotensive response, and those showing a rise of 6 mm. Hg or more were reported as showing a hypertensive response. The maximum rise in blood pressure was 45 mm. Hg, and the maximum drop was 36 mm. Hg. With sodium amidotrizoate 47.5% of the patients showed a hypotensive response, 36.7% a normotensive response, and 15.6% a hypertensive response. In the 50% sodium acetrizoate series 31.6% had a hypotensive response, 44.7% a normotensive response, and 23.7% a hypertensive response.

The relation of untoward reactions to blood pressure changes was also studied. In the sodium amidotrizoate series there was an incidence of reaction of 39.5% in those patients who showed a hypotensive response, 23.8% in those showing a normotensive response, and 17.7% in those showing a hypertensive response. In the 50% sodium acetrizoate series there was an incidence of 40% reactions in the hypotensive group, 32% in the normotensive group, and 33% in the hypertensive group.

These findings indicate that if a hypotensive response occurs, the incidence of reaction with sodium amidotrizoate is the same as with 50% sodium acetrizoate. Also the incidence of reaction is greater if hypotension results. No correlation was found between the type of reaction and the blood pressure response.

Quality of Urograms as Related to Reaction.—The effect of the reaction on the various aspects of the urographic images was also considered. It was found that the best studies were obtained in those patients in whom sodium amidotrizoate was injected without a reaction. The results in those patients who received sodium amidotrizoate and who experienced a reaction were only slightly better than the results in those receiving 30% sodium acetrizoate and in whom no reaction occurred. The poorest results were obtained in the group who recieved 30% sodium acetrizoate and experienced a reaction.

Quality of Urograms as Related to Blood Pressure Changes.—No comparison of the quality of the urographic studies as related to the blood pressure response was made except for nephrogram production and presence of tubular opacification in the group who received sodium amidotrizoate. Some tendency toward a decrease incidence of nephrogram production was indicated in the hypotensive group. Very little distinction could be obtained between the normotensive and hypertensive groups. The incidence of tubular demonstration did not vary with blood pressure change.

Quality of Urographic Films.—In evaluating the roentgenographic studies, it was found that sodium amidotrizoate consistently produced higher readings in four categories; these were percentage of ureteral visualization, caliceal density, renal pelvis density, and extent of caliceal demonstration. It was realized that the density of the caliceal and pelvic outlines depended upon the size of these structures. No consistent improvement in grading on the size of these structures resulted from the use of sodium amidotrizoate. This indicates an actual increased opacification by the sodium amidotrizoate.

Figures 2 through 5 illustrate (1) comparative gradings of the quality of the urographic films by the two observers and (2) the percentage of the examinations falling into each of the gradings, 1 through 4, for the categories (ureteral visualization, caliceal density, renal pelvis density, and extent of caliceal demonstration). No consistent differences were noted between the two media as regards size of renal pelvis and calices, nephrogram production, and tubule visualization, and these features are therefore not included on the figures.

Evaluation of the density of the renal pelvis revealed that 78% of the studies were graded as 3 or 4 when sodium amidotrizoate was used. The maximum comparable grading by either observer with 30% sodium acetrizoate was 63%.

In grading caliceal density, one observer

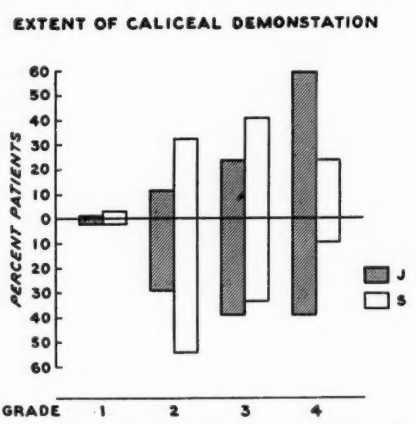


Fig. 2.—Extent of caliceal demonstration. This graph shows the percentage of the total number of patients examined using sodium acetrizoate 30% and sodium amidotrizoate 50% which were recorded as Grades 1, 2, 3, and 4. The bars extending below the line represent the percentage of the patients in whom sodium acetrizoate was used. The bars above the line represent the percentage of patients in whom sodium amidotrizoate was used. The striped bar shows the gradings by one of the observers, and the clear bar represents gradings by the other observer. The graph shows an improvement in the extent of caliceal demonstration by the use of sodium amidotrizoate 50% as compared with sodium acetrizoate 30%.

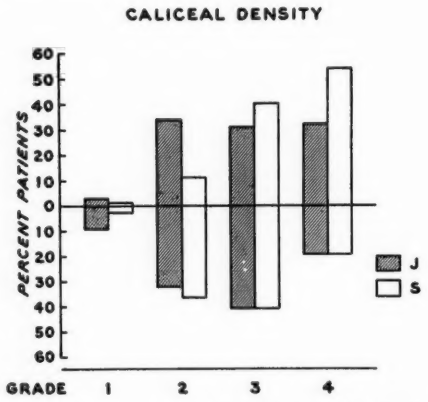


Fig. 3.—Caliceal density. This graph demonstrates the improvement in production of caliceal density by the use of sodium amidotrizoate 50% as compared with the sodium acetrizoate 30%. The meaning of the graphing represented is the same as for Figure 2.

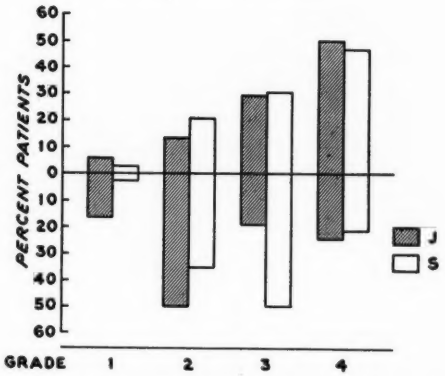


Fig. 4.—Renal pelvis density. This graph shows a distinct improvement in the density produced in the renal pelvis by the use of sodium amidotrizoate.

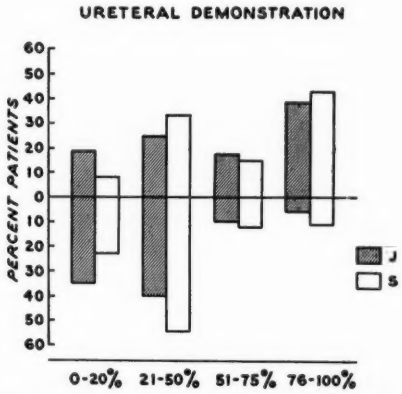


Fig. 5.—Ureteral demonstration. This graph shows that there is marked improvement in the amount of ureter demonstrable by the use of sodium amidotrizoate.

recorded 94% of the sodium amidotrizoate films as Grade 3 or 4; the same observer gave 61% of the 30% sodium acetrizoate group Grade 3 or 4. The comparable figures for the other observer were 64% with sodium amidotrizoate and 61% with 30% sodium acetrizoate. In the grading by the second observer, however, the percentage in Grade 4 for the two media showed 32% with sodium amidotrizoate and 20% with 30% sodium acetrizoate.

The comparison of caliceal extent showed 65% graded 3 or 4 with sodium amidotrizoate against 43% for 30% sodium acetrizoate by one observer; the other observer's figures showed 83% graded 3 or 4 with

sodium amidotrizoate and 78% graded 3 or 4 with 30% sodium acetrizoate.

If the grading of the ureter visualization is considered in groups of 0%-20%, 21%-50%, 51%-75%, and 76%-100%, the gradings which fall into these categories with sodium amidotrizoate are 8%, 33%, 16%, and 43% as compared with 30% sodium acetrizoate gradings of 23%, 54%, 12%, and 11% as judged by one observer. The comparable gradings by the other observer were 19%, 25%, 18%, and 38% for sodium amidotrizoate and 36%, 40%, 10%, and 14% for 30% sodium acetrizoate.

Thus for sodium amidotrizoate an average of 58% was recorded as showing more than 50% of the ureters, and for 30% sodium acetrizoate an average of 24% fell into this range.

The value of demonstrating the ureters as completely as possible is apparent in attempting to evaluate abdominal masses, levels at which narrowing has occurred, and possible anomalous course of the ureter. The use of sodium amidotrizoate eliminates the need for abdominal compression which, according to Sandström,[4] tends to produce untoward reactions.

Comment

The initial purpose of this investigation, the evaluation of the sodium amidotrizoate 50% as compared with sodium acetrizoate 30% and sodium acetrizoate 50%, was accomplished and indicated the superiority of the sodium amidotrizoate 50% in the degree of reaction at a comparable concentration and a better roentgenographic concentration than the lower concentration. It is of interest that one of the outstanding differences lay in the extent of ureteral demonstration, and an attempt was made to determine the possible cause for such superiority.

Apparently, one factor is the decreased local irritative effect of sodium amidotrizoate on the urinary collecting system. In support of this thesis is the observation that the 30% sodium acetrizoate was more rapidly excreted from the renal pelvis and ureter during the period covered by the usual urographic examination. The local irritative effect is a stimulus to increased peristaltic activity of the renal pelvis and ureter with resultant increased rate of drainage into the bladder. Additional studies conducted by the manufacturer of sodium amidotrizoate and reported in the booklet on additional clinical and laboratory data [2] show a decreased amount of Trypan-blue staining of the cerebral hemispheres in rabbits after injection of sodium amidotrizoate. While the considerations in this latter study are not identical with those encountered in pyelography, evidence is still presented to indicate decreased local effect by sodium amidotrizoate.

A second factor is the systemic reaction to the type of medium used. Wolf [6] has shown that painful stimuli will decrease the iodopyracet (Diodrast) clearance of plasma and decrease the amount of urine flow. The quality of the urographic study would suffer if severe discomfort were present, because of the decreased filling of the intrarenal structures and the decreased degree of density which could be produced. Schottstaedt [5] has shown in his studies that fear and pain produce variations in the amount of urine formation, which finding would also substantiate the thesis that those media which produce the slighter degree of reaction would produce the better urographic films.

The incidence of reactions which occurred when sodium amidotrizoate is used is higher than that reported by Root and Strittmatter,[3] who found less than 10%. The incidence in this series was approximately 30%.

The reactions recorded by Root are much the same as those evaluated here with the addition in his studies of bad taste as a reaction, which was not recorded in the present group. Root used a dose schedule of 25 cc. per patient as compared with 30 cc. or more used in the present series. The additional 5 cc. used in most of the

patients in this investigation probably does not account for the increased degree of reactions.

In the evaluation of urographic studies it must be remembered that it is impossible to evaluate the ureter and renal structures in their physiologic state. Any intravenous injection will produce some degree of a general systemic reaction. This reaction may be only temporary but of sufficient degree to influence the reactivity of the renal structures and ureters and thus give a distorted appearance of the actual status of these organs.

Summary

Sodium amidotrizoate in 50% concentration has produced consistently better urograms than has 30% sodium acetrizoate. The incidence of reaction to sodium amidotrizoate was found to be higher than reported elsewhere,[3] but the severity of reaction was much less than with 50% sodium acetrizoate, as judged by the frequency of nausea and vomiting.

The urographic features which were strikingly improved were caliceal extent, caliceal and renal pelvis density, and extent of ureteral visualization. The possible causes for such difference have been suggested as related to local irritative effect and systemic reaction.

A higher incidence of reactions is noted in those patients who received sodium amidotrizoate and who showed a hypotensive response than in those patients with a hypertensive response or with no change in blood pressure readings.

Winthrop-Stearns, Inc., and the Mallinckrodt Chemical Works provided the materials used.

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Secondary Tumors of the Penis

Report of Four Cases

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Secondary tumors of the penis are admittedly rare. However, like many so-called pathological curiosities the number of reported cases in the literature belies their true occurrence, and in any large autopsy series secondary tumor infiltrations of the corpora cavernosa will be found sporadically.

In a review of the literature of the last 70 years, we have found 59 cases of metastatic infiltrations of the penis. These are summarized in the Table according to the sites of origin. Primary tumors have arisen from the prostate, bladder, rectum, kidney, testis, lung, liver, nasopharynx, and ilium. In the majority of cases the metastatic penile tumors have originated in the prostate, bladder, and rectum. Four additional cases of secondary tumor infiltrations of the penis are being reported: one from the rectum, one from the bladder, and two from the prostate.

Report of Cases

CASE 1.—A 47-year-old white man had a total colectomy in 1948 for polyposis of the colon and carcinoma of the rectum.

Seventeen months later there began progressively severe deep perineal pain. Examination in July, 1950, revealed an obese man who had a well-healed left rectus abdominal scar and a functioning ileostomy. There were no abdominal masses and no palpable inguinal nodes. An undescended right testis could not be palpated. Urinalysis was negative, and

Sites of Origin of Metastatic Infiltrations of the Penis

Prostate 17 Cases	Bladder 14 Cases	Rectum 13 Cases
Tuffier—1885	Paschkis—1929	Niewiesch—1933
Young—1926	Neumann—1931	Matheson—1935
Frontz, Alyea—1928	Kessel—1934	Stein, Hantsch—1938
Paglieri, Schiappapietra—1928	Peacock—1938	Kerr, Gillies—1944
Guibal, Pavie—1929	Wattenberg—1944	Melicow, Ganem—1946
Nogues—1929	Melicow, Ganem—1946 (2 cases)	Cattell, Mace—1951
Martin, Laval—1931	Musiani—1947	Thompson—1950
Cecil—1936 (2 cases)	Fort, Bailey, Kicklighter, 1951	Bowersox, Frerichs—1952
Peters, Huntress—1938	Berard, Burne—1953	Ney—1952
Waller, Hellwig—1953	Poutasse—1954 (2 cases)	Boyd—1954
Espinosa, Mahony, Albano—1954	Hamm, Weinberg—1955	Poutasse—1954
Wilson, Horton, Horton—1954	Kaufman, Kaplan—1955	Kaufman, Kaplan—1955
Hamm, Weinberg—1955 (2 cases)		
Kaufman, Kaplan—1955 (2 cases)		

Kidney 7 Cases	Testis 6 Cases	Lung 3 Cases
Reinecke	Froin, Pignot, 1910	Staffieri, Kruse, Levit—1943
Begg—1928	Bergeret—1914	Garlick—1952
Craig—1941	Ricaud—1927	
Melicow, Ganem—1946	Garafalo—1931	
Burrell—1948	Santy—1933	
Henderson—1950	Hamm, Weinberg—1955 (lymphosarcoma)	
Klinger—1951		

Liver	Nasopharynx	Ilium
Gadiat—1930	Markson, Stoops, Canter—1949	deLorenzo, Cordeiro—1944

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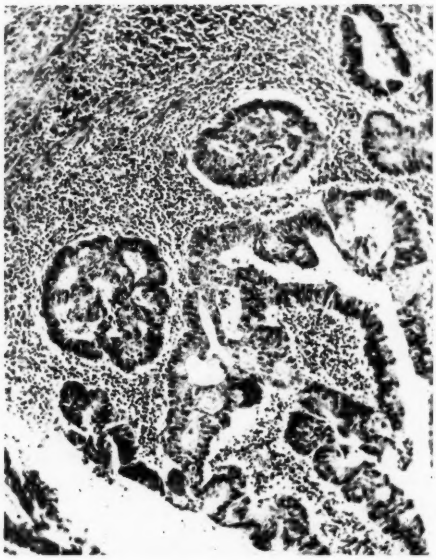


Fig. 1.—Microscopic morphology of adenocarcinoma of the rectum.

the blood urea nitrogen was 10 mg/100cc. Roentgenographic studies of the chest, lumbar vertebrae, and pelvis were negative. Sitz baths and local procaine injections were given for the perineal pain. These measures were of transient benefit.

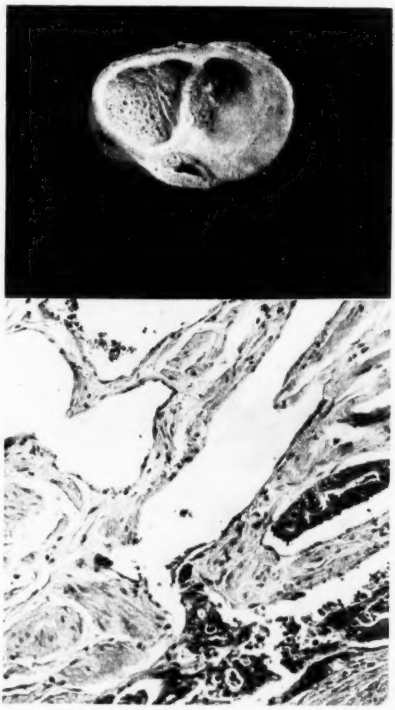
On July 14, 1950, laparotomy revealed a 2.5 cm. area of scarring deep in the cul-de-sac, biopsy of which disclosed adenocarcinoma. On Sept. 1, 1950, a hard nodule 3 cm. in diameter was noted in the midportion of the right side of the penile shaft. Subsequently, a massive tumor along with the prostate was removed perineally. The bladder was found to be uninvolved. A perineal sinus tract developed postoperatively. Roentgen therapy was given to the perineum and to the penile metastasis. The patient became incontinent of urine, developed massive edema of the lower extremities, and died on Dec. 25, 1950.

At autopsy metastatic nodules were found on the peritoneum and in the liver, small bowel, and mesenteric lymph nodes. Neoplastic infiltration of the corpus cavernosa was found. It extended crescentically as a laterally placed broad plaque of stony, hard, gray-white neoplasm that measured $3.5 \times 3.0 \times 1.5$ cm. along the capsular surface of the corpus and by continuity, invaded the spongy substance beneath for a distance of 1.5 cm. This nodule was discrete, and no extension along lymphatic or blood vascular channels was encountered proximally. It permeated the venous channels of the dorsolateral aspect of the corpus and delicately infiltrated its fibromuscular septa. Its extension into Buck's fascia appeared to be interstitial but was found within lymphatics occasionally. The marginal blood vascular sinuses did not contain thrombi. Figure 1 shows the microscopic morphology of the rectal carcinoma. Figure 2 demonstrates the gross and microscopic appearance of the penile metastasis. The cytologic identity with the parent tumor is clearly evident.

Case 2.—A 60-year-old Negro began experiencing hematuria, nocturia, dysuria, and frequency in January, 1946. In another hospital a diagnosis of carcinoma of the bladder was made. In March, 1946, cystotomy with radon seed implantation was done. He was readmitted several months later because of progressive urinary symptoms, weakness, and weight loss. Tenderness over the urinary bladder was found. The right inguinal lymph nodes were enlarged, fixed, and hard. The urine contained many red and white blood cells. Intravenous urography revealed an early left-sided hydronephrosis, and cystoscopy disclosed diffuse carcinomatous infiltration of the bladder.

The histopathologic studies showed a typical transitional-cell carcinoma (Grade 2) arranged in broad nests and sheets of cells. The latter were

Fig. 2.—Gross and microscopic appearance of metastases in corpus cavernosum.



fairly uniform and contained large granular nuclei. Occasional clusters of tumor cells had unusually large hyperchromatic nuclei. The cytoplasm was scanty and delicately stippled. There was an occasional attempt to form spaces lined by neoplastic transitional-cell epithelium. Mitoses were frequent and extension into lymphatics was easily demonstrated.

The patient died uneventfully on Sept. 12, 1946. At autopsy tumor infiltration about the suprapubic cystotomy was found. The bladder, rectum, and pelvic retroperitoneal tissues were firmly fixed to one another by scar and neoplasm. The bladder wall was thickened by a mass of fungating necrotic tumor. The bladder dome was uninvolved. There were metastases to the right inguinal lymph nodes. In the shaft of the penis there was a discrete, firm gray-white tumor nodule measuring 1.5 cm. in the greatest diameter. It was firmly fused with Buck's fascia and extended outward into the spongy vascular substance of the corpus.

CASE 3.—A 77-year-old white man had a transurethral resection of the prostate and orchiectomy in October, 1950, for invasive carcinoma of the prostate. Recurrence of urinary symptoms culminated in acute retention in October, 1951. At this time, the prostate was stony hard and fixed. The acid phosphatase was 9.6 units (Bodansky), and the alkaline phophatase was 6 units. Diffuse osteoblastic metastases throughout the pelvis, sacral bones, and lumbar vertebrae were found. Intravenous urography revealed early right-sided hydronephrosis. Transurethral resection of the prostate was done. The pathological diagnosis was adenocarcinoma of the prostate. He was treated with diethylstilbestrol (Stilbestrol), 5 mg. daily, until death.

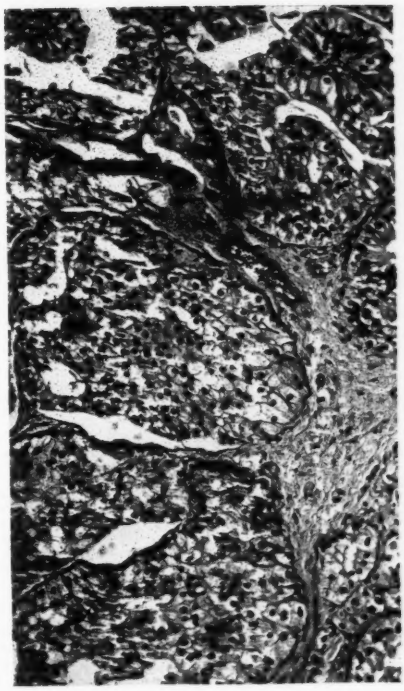


Fig. 4.—Photomicrograph (× 400) of the primary tumor arising in the prostate.

Fig. 3.—Metastatic inguinal lymph node involvement and areas of penile metastases.

He was readmitted on Feb. 18, 1952, because of several episodes of gross hematuria and generalized purpura. The prostate was stony hard and three times normal size. Acid phosphatase was 25.5 units, the alkaline phosphatase, 9.3 units. Firm metastatic nodules were found in both inguinal regions. Several hard nodules were felt on the dorsum of the penis deep to Buck's fascia. The enlarged inguinal lymph nodes and areas of penile involvement are shown in Figure 3. Biopsy revealed metastatic carcinoma in the inguinal lymph nodes and corpora cavernosa. The patient's course was marked by epistaxis and azotemia. This was considered secondary to lower ureteral obstruction by prostatic carcinoma. Large doses of cortisone did not alter the course, and the patient died on May 5, 1952. At autopsy, he was found to have primary adenocarcinoma of the prostate with diffuse metastases to the liver, inguinal lymph nodes,

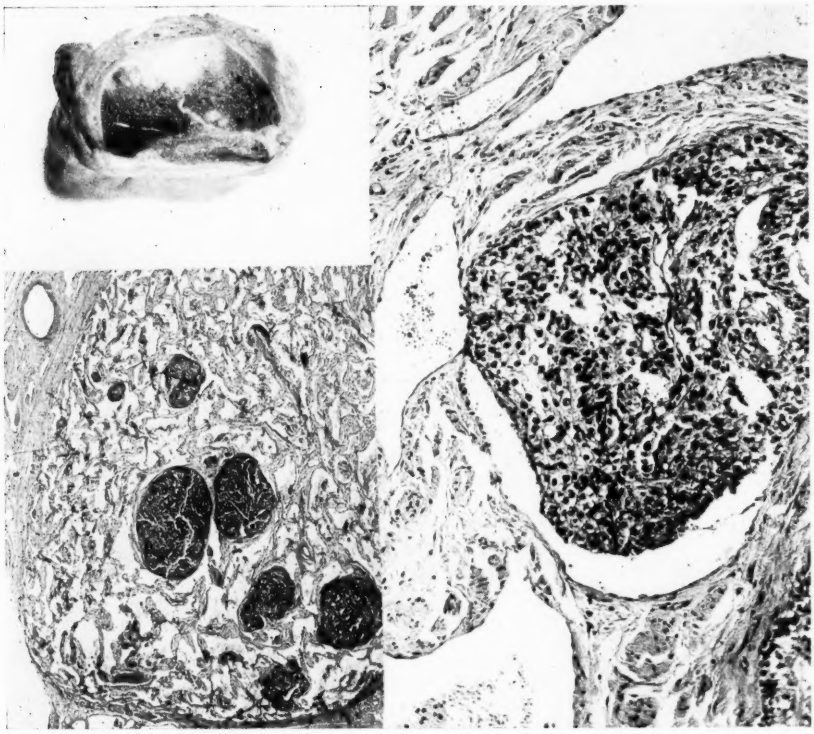


Fig. 5.—Gross and microscopic appearance (× 100 and × 400) of metastatic penile nodules.

and penis. One penile metastasis was situated dorsally, sharply defined by the tunica albuginea of the penis, and extended radially into both corpora cavernosa. Two additional foci of neoplasm were found in the right corpus ventrally. There was no apparent continuity between the prostatic neoplasm and that of the penis. Figure 4 is a photomicrograph of the primary tumor arising in the prostate. Figure 5 demonstrates the gross and microscopic appearance of the metastatic penile nodules.

The prostatic tumor cells uniformly showed vacuolated cytoplasm with large, granular nuclei. There were many mitoses. The permeation of interstitial and perineural lymphatics was extensive. The biopsy and autopsy involvement of the penis were identical. They showed large, conglomerate masses of tumor cells, identical with those within the prostate, filling dilated vascular channels and occasionally permeating their walls. A rare organizing thrombus was observed adjacent to such neoplastic infiltration.

Case 4.—A 57-year-old white man was admitted on Sept. 8, 1953. Three years previously a transurethral resection was performed elsewhere, and it demonstrated primary carcinoma of the prostate. He had taken diethylstilbestrol daily since the operation. For three months prior to admission he had increasing urinary frequency, dysuria, small stream, and persistent swelling of the left leg. The testes were atrophic, and both breasts were enlarged because of estrogen administration. The prostate was found to be enlarged to twice normal size, very hard, irregular, and fixed. There were several discrete, hard nodules on the dorsum of the penis, close to the base.

Urinalysis revealed many pus cells. The acid phosphatase ranged from 0.6 to 0.8 units, and the alkaline phosphatase was 6.4 units. Blood urea nitrogen was 24 mg/100cc. Roentgenographic skeletal survey revealed no metastases. An intravenous urogram was negative. On Oct. 2, 1953, a transurethral resection of the prostate established the diagnosis of primary adenocarcinoma. At the same time, biopsy of the shaft of the penis and bilateral orchiectomy were performed. The prostate revealed a primary carcinoma forming broad cords and nests of tumor cells with irregularly distributed gland-like spaces. The biopsy specimen of the penile metastases showed identical neoplasm per-

meating the vascular channels. The portion of the corpus involved was adjacent to Buck's fascia. Within the fibromuscular septa and focally between Buck's fascia there were isolated strands of neoplastic cells.

On Oct. 23, 1953, the patient was treated with radioactive chromic phosphate introduced into the prostate through the bladder. The patient recovered from this procedure without incident and was discharged on 5 mg. of diethylstilbestrol daily. He was last seen on Dec. 2, 1953, at which time he complained of dysuria but was having no other difficulty. He was lost to further follow-up.

Comment

Numerous theories of the pathways that must be traversed by tumor cells that reach the corpus cavernosum of the penis have been proposed. It has been postulated that tumors arising from the bladder or rectum may involve the corpus by direct extension through the ischiorectal fossa, penetrating the urogenital diaphragm and Colles' fascia into the superficial perineal space. The theory of spread via Batson's plexus of veins has numerous followers and seems the most tenable explanation for the retrograde spread of prostatic and bladder malignancies. Batson demonstrated intercommunication between the pelvic, paravertebral, and vertebral veins. The dorsal vein of the penis communicates directly and through collateral channels with this venous system. To substantiate this theory it has been noted that most metastases in the penis are on the dorsum in the distribution of tributaries of the dorsal vein. Spread via lymphatic channels has also been proposed. To explain the spread of rectal carcinoma to the penis, it has been suggested that lymphatic channels of the inferior hemorrhoidal group communicate with those of the perineal region and anastomose with those of the inguinal region. Other lymphatic channels accompanying the internal pudendal blood vessels join with those about the inferior hemorrhoidal venous plexus. Arterial embolic spread of cancer cells may occasionally account for metastatic penile tumors. This may be the mode of transmission from primary neoplasm of the liver, kidney, lung, and nasopharynx. The clinical significance of secondary malignant infiltration of the penis lies in differentiating such lesions from primary neoplasms. The latter offer opportunities for clinical cure. Secondary tumors must be differentiated from such innocent conditions as fibrous induration of the corpus cavernosum (Peyronie's disease).

Although metastatic cancers involving the corpus cavernosum are admittedly rare, physicians should be aware of the occurrence of this entity. Most of the reports emphasize the late appearance of penile metastases. Priapism associated with metastases to the corpus cavernosum has been reported frequently. This relationship occurred in approximately one half of the collected cases. Priapism was not present in any of our cases. Encroachment upon the urethra by secondary tumors of the penis with urinary symptoms has also been reported.

Since metastatic tumors of the penis usually occur late in the course of malignant disease, definitive treatment is impossible. Amputation of the penis or local excision of metastatic lesion have been reported.[9] In the majority of cases, however, palliative treatment is the only recourse. When the carcinoma is metastatic from the prostate, palliation may be moderately effective.

Summary

A total of 59 cases of metastatic tumors involving the penis have been collected and 4 additional cases are reported bringing the total to 63. The sites of origin of the carcinomas are the prostate in 17, the bladder in 14 and the rectum in 13 cases. Two cases of metastatic spread to the corpus cavernosum from the prostate, one case of metastatic spread from carcinoma of the bladder, and one case of metastasis from carcinoma of the rectum make up our group.

Secondary tumor infiltrations of the penis should be differentiated from primary tumors, much as melanosarcoma and carcinoma of the urethra, and from fibrous induration of the corpus cavernosum.

Since metastatic tumors of the penis

usually occur late in the course of cancer spread, palliative treatment is necessarily the only recourse. Amputation of the penis or excision of the metastatic nodule may be done for palliation, but survival is rarely prolonged by such treatment.

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Fractures of the Ankle

VI. Follow-up Studies

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In previous papers* in this journal Lauge-Hansen described his classification of fractures of the ankle according to their pathologic anatomy. He also explained his methods of reduction based on the genesis of these fractures and his technique of immobilization, which gives the best possibility of maintaining the anatomic relationship after reduction. The genetic roentgenologic diagnosis was discussed in a journal of roentgenology.[2]

The present paper is a report on the results obtained in a large series of patients treated by Lauge-Hansen's methods of reduction and immobilization, and these results are compared with those obtained by the methods which were previously used in this country. The evaluation of the effectiveness of these methods of treatment is based on the results as evidenced by roentgenograms taken immediately after reduction and on the results of follow-up examinations of the patients. The follow-up studies comprised questioning of the patients (subjective result), a clinical examination of the position and range of motion of the ankle joint and foot and an evaluation of the gait (clinical result), and roentgenologic studies of the affected ankle joint and the unaffected fellow joint (roentgenologic result). These studies were performed at least three years after treatment. Some of the patients were examined twice, viz., 12-18 months and 3-5 years, respectively, after treatment. These double examinations showed that the condition of the patients may be expected to have become stationary after the lapse of three years, in most cases even as early as one year after treatment. In the survey which follows, only the results from the last follow-up examination are considered.

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1. Case Material

The survey comprises patients who were treated for fractures of the ankle during a five-year period in the Central Hospital, Randers, in Denmark. The patients were treated according to the technique of Lauge-Hansen, most of them by me in close collaboration with Lauge-Hansen. The treatment was actually a surgical experiment inasmuch as it was designed to show how good results could be obtained by closed reduction by Lauge-Hansen's technique; open reduction and osteosynthesis were purposely avoided, even in cases in which closed reduction did not give perfectly normal anatomic relationship. The justification of this experiment was that so far no material had been available in which it was shown how exact the reduction of a malleolar fracture should be in order to give a good end-result. As the principal objects of this study were to clarify what symptoms malleolar fractures may leave and the relation of these symptoms to the roentgenographic appearance after reduction, all patients who had complicated fractures or other lesions which might influence the condition of the patients were excluded. This applies to (*a*) patients with epiphyseal separation; (*b*) patients with pronation-dorsiflexion fractures, because a method of treatment of this type of fracture has not yet been worked out in detail, and (*c*) patients with Stage V and Stage VI fractures, because the tibial fracture which is present in these stages renders special therapeutic measures necessary. Thus, the series comprises a total of 232 adult male and female patients.

Patients from two large provincial hospitals who were treated before the introduction of Lauge-Hansen's methods served as controls. The treatment of malleolar fractures in these two hospitals was roughly representative of the methods which were previously used in Denmark and consisted in manual reduction, in some cases without anesthesia; immobilization in an unpadded plaster cast, or, in rare cases, open reduction and osteosynthesis. The three aforementioned groups of patients were also excluded from the control series, which, after this exclusion, comprised a total of 239 adult male and female patients.

The age and sex distribution of the two series showed good agreement. The follow-up examinations and the evaluation of all available roentgenograms were made by me. The follow-up studies comprised 194 and 197 patients, i.e., 93% and 91%, respectively, of the patients from the two series who were alive and lived in Denmark at the time of the follow-up examination.

2. Methods of Evaluation

The ultimate outcome of the treatment is considered under two headings in this survey, viz., the subjective result and the clinical result.

A. Subjective Result. — The subjective result is based on an evaluation of the patient's own statements as to discomfort from the fracture irrespective of the presence or absence of a demonstrable basis for such complaints.

The subjective result was described as good in all cases in which the patients had no discomfort from the fracture or only mild discomfort following extra strain of the ankle joint; as medium in all cases with severe discomfort on extra strain, so that the patient had "to pay regard to the leg," or with mild daily discomfort which did not prevent the patient from attending to his usual work at the same remuneration as before the accident, and as poor in all cases with reduced working capacity due to sequelae of the fracture of the ankle. The last of these three groups includes cases in which the patient had had to make a change of occupation or in which the wages were reduced or could be maintained on the former level only by obligingness from employer or fellow-workers and, finally, cases in which special footwear or other special measures were necessary to maintain the former level of wages.

A survey prepared on these lines gives an impression not only of the social importance of malleolar fractures but also of the capacity of the injured joint. However, the results of such an evaluation are to a very great extent dependent on the conditions of life of the individual patient and his capacity for adjustment. These factors are so variable that the subjective result cannot be used as the only basis for an assessment of the ultimate results of treatment but must be supplemented with an assessment of the clinical result.

B. Clinical Result.—The clinical result is based on an evaluation of the appearance and range of motion of the injured joint and of the gait. In this way it shows the extent to which it has been possible to restore normal anatomic and physiologic conditions of the joint.

The clinical result was described as good in all cases in which union of the fragments without deformity of the ankle joint or foot had been obtained and in which the gait was normal and the range of all movements of the ankle joint and foot was at least one half of that of the unaffected side; as medium in all cases in which the range of at least one of the movements of the ankle joint or foot was reduced to less than one half of that of the unaffected side but in which the gait was normal, with absence of deformity of the ankle joint or foot, and as poor in all cases with deformity of the ankle joint or foot, including patients with unilateral flatfoot or flatfoot which was considered more pronounced on the affected than on the unaffected side.

Some of the cases with disturbances in the gait or with flatfoot were so mild that little or no daily discomfort was caused to

the patients. In this way a certain discrepancy beween the subjective and clinical results arose, but the classification was nevertheless maintained in order to avoid an assessment of the severity of the disturbances in the gait or of the flatfoot, because such an assessment to a greater extent would depend on the attitude of the examiner than the mere decision whether or not one of these complaints was present.

The limitations of motion were classified on the basis of the view that a reduction to less than one-half of the range of the unaffected side will involve discomforts if the patient exposes his ankle joint to extra strain, even if daily routine does not force him to do so. The range of motion varies within wide limits in the various age groups,[6] and so a normal value for the individual movements cannot be fixed, for which reason a comparison between the movements on the affected and the unaffected side was made.

Soft-part thickening around the ankle joint was not included under "deformity of the ankle joint," because such thickening, even when it is only moderate, will always occur in combination with other clinical signs of sufficient severity to classify the result as poor. Small cushion-like thickenings in front of or behind the malleoli were frequently observed, even in patients who had no discomforts from the fracture, but they were not included in the evaluation, because it is impossible to differentiate them from physiologic thickenings and because they are only of cosmetic importance.

As already pointed out, the two methods of evaluation do not give absolutely identical results, but nevertheless they show fairly good agreement. Of the 471 patients in the two series, 285 showed a good clinical result. Of these, 259 (91%) also revealed a good subjective result. A good subjective result was obtained in 283 patients. In 259 of these, the clinical result was also good. A poor subjective result was seen in 14 patients; among these, the clinical result was poor in 12 and medium in 2. The clinical result was poor in 60 patients; among these, the subjective result was poor only in 12, while it was medium in 37 and good in 11. This discrepancy is due to the fact that some cases of flatfoot or disturbances in the gait were so mild that they did not give rise to discomforts in daily life.

C. Roentgenologic Result. — The roentgenologic classification of the results of the reduction of the fractures was made as follows:

The roentgenologic result was described as poor in all cases with displacement of the talus, irrespective of direction or degree, because the objective if the reduction of the talus is to restore the congruity of the articular surfaces.

Displacement of he malleoli does not lead to direct incongruity of the weight-bearing articular surfaces, unless the lateral malleolus is displaced medially or the medial malleolus is displaced laterally, because such displacements occur only in the presence of a concurrent displacement of the talus.

In the presence of lateral displacement of the lateral malleolus or medial displacement of the medial malleolus the malleolar fork (tibiofibular mortise) is widened, so that the talus may become displaced laterally, and when a malleolar fragment is displaced in the sagittal plane rotation of the talus may occur. Distal displacement of a malleolar fragment will lead to laxity of the ligament which is attached to the malleolus, which, in turn, may result in instability of the joint. Accordingly, if treatment leads to one of these types of displacement, the result cannot be described as good. As the possibility of displacement of the talus increases with the magnitude of the displacement of a malleolar fragment, the roentgenologic result was classified as medium in cases in which the lateral displacement of the lateral malleolus and/or the medial displacement of the medial malleolus was up to 2 mm. In the presence of a larger displacement in one of these directions, the roentgenologic result was described as poor.

Cases with dorsal displacement of the lateral malleolus or anterior displacement

of the medial malleolus were classified as roentgenologically good, provided that the displacement did not exceed 2 mm. Cases with displacement amounting to 2-5 mm. in one of these directions were put down as roentgenologically medium, while those with larger displacement in the sagittal plane were described as poor.

Displacement of a fragment at the posterior margin of the tibia will always lead to incongruity of the weight-wearing articular surfaces, except when the fragment is very small. Considering that the displacement almost invariably occurs in the dorsal or proximal direction, and that the fragment in most of the cases under consideration here constituted only a small proportion of the articular surface, this incongruity is scarcely of decisive importance for the end-result, but the displacement of a fragment of the posterior margin of the tibia will—just like the displacement of the lateral malleolus—prevent the reduction of the talus. Accordingly, in the classification of patients with displacement of a fragment of the posterior margin of the tibia, the roentgenologic result was described as good when the dorsal and/or proximal displacement did not exceed 2 mm., as medium if the displacement amounted to 2-5 mm., and as poor if the displacement exceeded 5 mm.

In the presence of displacement of several fragments, the case was classified on the basis of the fragment which gave the poorest result.

The roentgenologic classification was supported by the experience gained in the follow-up examinations, by which it could be demonstrated that a statistically significant correlation existed between the changes in the positions of the lateral malleolus, the fragment of the posterior margin of the tibia, and the talus. I also demonstrated this correlation both experimentally[4] and by autopsy on a patient who died a few days after she had sustained a pronation-eversion fracture. In addition, the experiments showed that if reduction of the posterior margin of the tibia was prevented, neither the lateral malleolus nor the talus could be reduced to a tolerably correct position. The follow-up examinations revealed statistically significant differences in the subjective and clinical results obtained in patients whose fractures had been reduced to roentgenologically good, medium, and poor position, respectively.

The reason why the number of discomforts increases with the degree of displacement of a fragment, even though no displacement of the talus can be demonstrated, cannot be deduced from the material. The discomforts may be due to a displacement of the talus which is so small that it cannot be recognized in the roentgenogram, or the displacement may be present only at intervals. The roentgonograms in this series were taken in the usual way, avoiding weight-bearing of the ankle joint. However, it is likely that certain dislocations of the malleoli only allow of so small abnormal movements of the talus that its displacement becomes manifest only when weight-bearing is allowed, just as is seen in the valgus position of the heel in some cases of pes planovalgus.

The follow-up studies revealed good anatomic relationship in 237 patients. Of these patients, 28 were overweight. In an analysis of the results for the 209 patients of normal weight it was not possible to demonstrate that the type of fracture or the number of lesions present as expressed by the stage of the fracture had any influence on the end-result. Nor did the ages of the patients seem to exert any influence on the end-result; a good end-result was just as frequent in elderly patients with a high-stage fracture as in young patients with a low-stage fracture. The figures here are too small to allow of a statistical analysis, but they are so near to each other that they may be regarded as almost identical. Nor did the end-results obtained in cases with good position of the fracture on admission differ from those obtained in cases in which a good position was not achieved until after the reduction.

Also, as far as patients with medium position of the fracture at the follow-up

examination were concerned, the subjective and clinical results were identical for patients whose fractures were in a medium position on admission and those whose fractures were reduced to a medium position, irrespective of the type and stage of the fractures and the ages of the patients. It must therefore be justified to report the results of the reduction and of the follow-up studies for each of the two series collectively, regardless of the type and stage of the fractures and the ages of the patients. On the other hand, it is necessary to consider the position of the fractures on admission in the evaluation both of the results of reduction and those observed in the follow-up examinations.

Before these results are reported, the methods of reduction used must be briefly described. However, to understand these methods the reader must be familiar with the nomenclature used and the mechanism of production of the individual fractures, for which reason these are also briefly outlined below.

3. Nomenclature

Lauge-Hansen introduced a new nomenclature based on the principle that the name of each type of fracture indicates the movements which have produced the fracture. Each type of fracture is divided into various stages, so that the number of the stage indicates the number of lesions of bones and ligaments.

Each designation is composed of two words. The first word is either supination or pronation, by which the physiological movements are understood (in Anglo-Saxon literature called "inversion" and "eversion"). The second word is eversion, adduction, abduction, or dorsiflexion, all indicating the pathological movements between the talus and tibia (dorsiflextion, however, only an increase of the physiological movement beyond the normal). By eversion is understood an outward rotation of the talus and the foot around a vertical axis (in normal anatomic position), inversion is the reverse movement. Adduction and abduction are movements around a horizontal sagittal axis running at a varying height above the talus, so that these movements are not mere lateral displacements of the talus, but a combination of rotation and lateral displacement of this bone.

4. Types of Fracture and Methods of Reduction

Supination-Eversion Fractures

Mechanism of Production.—The supinated foot is everted, i.e., the tip of the foot is turned outward around a vertical axis. Owing to the supination, the ligamentum deltoideum is relaxed, and the first thing that happens is a lesion of ligamentum malleoli lateralis anterius (it may be accompanied by avulsion of a bone shell at one of the attachments (Stage I).

Now the lateral malleolus may rotate a little outward, but ligamentum interossenm and ligamentum malleoli lateralis posterius are intact. Continued outward rotation will therefore produce an oblique spiral fracture involving the lateral malleolus and the distal part of the fibula (Stage II).

By continued movement the pull exerted by ligamentum malleoli lateralis posterius will produce an avulsion fracture of the posterior lip of the tibia (or the ligament ruptures) (Stage III).

At that time ligamentum deltoideum is tightened and causes, if the movement is continued, a fracture of the medial malleolus (or the ligament ruptures) (Stage IV).

As appears from this account, some of the injuries may be either a fracture or a ligamentous lesion. However, within each type of fracture one lesion will always be present as a fracture if the stage in question has been reached. This fracture, which is generally situated in the fibula, may thus be used in the determination of the type.

The characteristic feature of the supination-eversion fracture is the oblique spiral fracture involving the lateral malleolus and the adjacent part of the fibula.

Reduction.—The principle underlying the reduction maneuvers is that movements of

the foot in the opposite direction and in the reverse sequence should be carried out.

Stages II, III, and IV: The anesthetized patient is placed in the dorsal position with the knee and hip of the fractured extremity flexed at right angles. The extremity is fixed by an assistant holding just proximal to the knee, and the operator grasps the heel with one hand and the forefoot and midfoot with the other. The reduction is then carried out as follows:

1. The movements producing the fracture are first performed, i.e., the supinated foot is turned outward and then plantarflexed. These movements "unlock" the fracture if it has become impacted.

2. By a very vigorous pull at the heel of the plantarflexed foot the proximal displacement of the fragments of the posterior lip of the tibia and lateral malleolus is corrected. The pull must be exercised in the longitudinal direction of the leg.

3. By pressure on the posterior surface of the heel the foot is brought forward while another assistant presses backward on the distal part of the leg. By this procedure the backward displacement of the two said fragments and of the talus is overcome.

4. The foot is inverted maximally, i.e., the tip of the foot is turned medially around an axis running in the longitudinal direction of the leg, by which the outward rotation of the lateral malleolus and the diastasis between the latter and the tibia are overcome; the foot is then pronated.

5. The plantarflexed foot is moved upward until it forms a right angle with the leg.

6. The unpadded plaster cast is then applied while an assistant holds the foot in the position described, which is done without difficulty if only the foot is kept carefully pronated all the time by a grasp around the metatarsal bones.

7. Facing the fractured foot, the operator places the bandaged extremity between his heteronymous arm and chest. While the plaster is hardening, he exerts a medial pressure on the heel region with the homonymous hand and a counterpressure on the medial malleolus with the palm of the other hand. In this way any remaining lateral dislocation of the talus and medial malleolus will be corrected. At the same time, the assistant pronates and inverts the anterior part of the foot so vigorously that it comes into maximal pronation and that the longitudinal axis through the leg runs through the third or fourth toe.

In Stage I (and Stage II without backward or proximal displacement of the lateral malleolus) the procedures numbered 4, 5, 6, and 7 will suffice. In Stages V and VI the tibial fracture is treated according to the usual principles; the malleolar fracture, as described above.

Supination-Adduction Fractures

Mechanism of Production.—The maximally supinated foot is supinated and adducted in the talocrural joint, thereby causing an avulsion fracture of the lateral malleolus (or a lesion of ligamentum calcaneofibulare) (Stage I).

Owing to the pressure exerted by the talus on the medial malleolus, the next lesion will be a fracture of the medial malleolus (Stage II).

The characteristic feature of this type of fracture is the transverse fracture of the lateral malleolus or a level with or distal to the articular surface of the ankle joint.

Reduction.—Stage I: After application of the plaster cast, the heel region is abducted and the forepart of the foot is pronated and everted a little while the plaster is hardening. Stage II: The foot is moved laterally and frontally; then same procedures are done as in Stage I.

Pronation-Eversion Fractures

Mechanism of Production.—When the foot is pronated, ligamentum deltoideum is tightened. If the foot is then everted, i.e., turned outward around a vertical axis, the results will be a fracture of the medial malleolus (or a lesion of ligamentum deltoideum) (Stage I).

Owing to the laxity caused hereby, there will, in addition to the eversion movement, also come a certain lateral effect of the pressure and ligamentum malleoli lateralis anterius and ligamentum interosseum will rupture (or bone shells may be torn off at the sites of the ligamentous attachments) (Stage II).

Now the fibula may rotate outward, more particularly the distal part, and at a varying height above the ankle joint a torsion fracture of the fibula is produced (it may be situated in the neck) (Stage III).

The pull at ligamentum malleoli lateralis posterius will then give rise to a fracture of the posterior lip of the tibia (or the ligament may rupture (Stage IV).

Further outward rotation may in some cases cause a torsion fracture of the tibia (Stage V).

The characteristic feature of this type of fracture is the high fracture of the fibula.

Reduction.—As in supination-eversion fractures, yet so that the foot is pronated and everted at the same time.

Pronation-Abduction Fractures

Mechanism of Production.—When the foot is maximally pronated, ligamentum deltoideum is tightened. If an additional pronation between the tibia and talus occurs, and/or the talus is displaced laterally, a fracture of the medial malleolus is produced (or ligamentum deltoideum ruptures) (Stage I).

Then the lateral pressure will exert its effect on the lateral malleolus and ligamentum malleoli anterius et posterius will rupture (or a bone shell may be torn off at one of the sites of attachment) (Stage II).

After this, the foot and the lateral malleolus may be carried further in the lateral direction, causing a bending fracture of the fibula a little above the ankle joint (Stage III).

The characteristic feature of this type of fracture is the bending fracture of the fibula a little above the ankle joint.

Reduction.—Stages I and II: After application of the plaster cast, the heel region is adducted and the forepart of the foot is pronated and inverted while the plaster is hardening. Stage III: The foot is moved frontally and medially, followed by the same procedures as in Stages I and II.

5. Results of Reduction

The results of reduction obtained in the two series appear in Table 1, in which the figures in parentheses indicate the number of patients in the control series. The patients with a "poor roentgenologic result" are divided into two subgroups, because it is believed to be of interest to show how often the talus was displaced and how often it was possible to correct this displacement.

TABLE 1.—*Results of Reduction*

	Roentgenologic Position After Reduction, Cases, No.*			
Roentgenologic position before reduction	Good	Medium	Poor, No Displacement of Talus	Poor, with Displacement of Talus
Medium	34 (0)	10 (37)		
Poor, no displacement of talus	1 (1)	3 (2)	2 (4)	0 (1)
Poor, with displacement of talus	58 (15)	11 (23)	3 (8)	5 (30)

* The number of control cases is given in parentheses.

The figures in Table 1 do not show complete agreement with those reported in the results of the follow-up studies, because those tabulated here also include cases which were not subjected to follow-up ex-

amination but in which roentgenograms were taken after the reduction.

None of the 37 patients in the control series with medium position of the fracture on admission obtained any improvement in the position. The explanation probably is that the hospital staffs in question regarded this degree of displacement as insignificant and therefore did not attempt reduction. On the other hand, it must be taken for granted that no efforts had been spared to reduce the fracture in all cases with displacement of the talus, for which reason an evaluation of the results for these patients must be supposed to give the best impression of the effectiveness of the two methods of treatment.

In the Lauge-Hansen series a good position of the talus and the fragments was obtained in 58 of 77 cases (75%), while this had been possible only in 15 of the 76 cases (20%) of the control series. In 30 of 76 cases (39%) of the control series the displacement of the talus persisted, as compared with only 5 of 77 cases (7%) of the Lauge-Hansen series. In three of these five patients a small displacement of the talus had been overlooked in the roentgenogram taken after the reduction, and not until the revision of the films at the follow-up examination was it detected that the reduction had not been perfectly correct. In addition, in a few cases of the Lauge-Hansen series we contented ourselves with a medium result of reduction, because it was considered that the additional advantage which it would be for the patients to have the fracture reduced to absolutely correct position would be small as compared with the discomforts of further attempts at reduction. In 5 of the 77 patients, two attempts at reduction were performed. In all five patients displacement of the talus was still present after the first attempt. Following the second attempt, the position was good in two patients and medium in two, while a small displacement of the talus still persisted in one, but this displacement was not recognized until at the follow-up examination.

Of the 76 patients in the control series, 14 were subjected to two attempts at reduction, which failed to give correct position of the talus in 10. Three patients were subjected to three unsuccessful attempts at reduction. In addition, wire extension through the calcaneus was used in four cases and osteosynthesis of various fragments in three.

Thus, Lauge-Hansen's methods of reduction not only give better results than those previously employed in Denmark but the results are obtained in a manner which causes less discomfort and pain to the patients.

6. Results of Follow-Up Studies

As might be expected, the improved results of reduction are also reflected in the evaluation of the subjective and clinical results of the follow-up examinations. As already pointed out, in order to obtain comparable materials it was necessary to make a subdivision of the results of the follow-up studies according to the position of the fracture on admission. The percentages stated in the results of the follow-up studies represent the percentages of the patients within the group in question who were alive and lived in Denmark at the time of the examination and in whom no causes of a possible poor result other than the malleolur fracture could be demonstrated.

(*a*) Patients with Good Position of the Fracture on Admission

Of the patients of the Lauge-Hansen series, 84 (87%) were followed up. In one a secondary displacement had occurred, giving a medium roentgenologic result and poor subjective and clinical results. Of the patients of the control series, 66 (90%) were followed up. Secondary displacement had occurred in two, giving a medium position in one and poor in one. The results for the patients with secondary displacement are included in the survey of the

TABLE 2.—*Results of Follow-Up Studies of Patients with Good Position of the Fracture on Admission*

	Result					
	Good		Medium		Poor	
	No.	%	No.	%	No.	%
Subjective result						
Lauge-Hansen series	74	88	9	11	1	1
Control series	52	79	13	20	1	1
Clinical result						
Lauge-Hansen series	76	90	4	5	4	5
Control series	52	79	6	9	8	12

follow-up studies given in Table 2.

In the Lauge-Hansen series, 73 of 84 patients (84%) showed good subjective and clinical results, while the corresponding figures in the control series were 49 of 66 patients (74%).

None of the differences demonstrated are statistically significant.

(*b*) Patients with Medium Position of the Fracture on Admission

Of the patients in the Lauge-Hansen series, 40 (100%) were followed up. The roentgenologic result was good in 30, medium in 8, and poor in 2.

TABLE 3.—*Results of Follow-Up Studies of Patients with Medium Position of the Fracture on Admission*

	Result					
	Good		Medium		Poor	
	No.	%	No.	%	No.	%
Subjective result						
Lauge-Hansen series	35	88	4	10	1	2
Control series	27	77	8	23	0	0
Clinical result						
Lauge-Hansen series	36	90	0	0	4	10
Control series	28	80	3	9	4	11

Of the control series, 35 patients (83%) were followed up. The roentgenologic result was medium in 34 and poor in 1.

The subjective and clinical results are given in Table 3.

Of the 40 patients of the Lauge-Hansen series, 34 (85%) showed good subjective and clinical results, while the corresponding figures in the control series were 21 of 35 patients (60%).

None of the differences demonstrated is statistically significant.

(*c*) Patients with Poor Position of the Fracture on Admission

Of the patients in the Lauge-Hansen series, 70 (97%) were followed up. The position of the fracture was good in 45, medium in 13, and poor in 12, including 9 with displacement of the talus.

TABLE 4.—*Results of Follow-Up Studies of Patients with Poor Position of the Fracture on Admission*

	Result					
	Good		Medium		Poor	
	No.	%	No.	%	No.	%
Subjective result						
Lauge-Hansen series	54	77	14	20	2	3
Control series	40	51	29	37	9	12
Clinical result						
Lauge-Hansen series	54	77	6	9	10	14
Control series	39	50	9	12	30	38

Of the patients in the control series, 78 (96%) were followed up. The position of the fracture was good in 15, medium in 24, and poor in 39, including 29 with displacement of the talus.

The subjective and clinical results are given in Table 4.

In the Lauge-Hansen series, 49 of 70 patients (70%) showed good subjective and clinical results, as compared with 33 of 78 patients (42%) in the control series. This difference is statistically significant, and the same applies to the difference in the number of patients with good subjective result and those with good clinical result. There is also a statistically significant difference in the number of patients with poor clinical results, while this is not the case with patients with a poor subjective result. However, the clinical result must be regarded as the most adequate expression of the results of treatment, because it does not depend on so many factors as the subjective result.

7. Symptoms

Some of the symptoms which are encountered in patients who have previously sustained an intra-articular fracture may be explained by the osteoarthritis which is

often demonstrated, while others must be referable to other sequelae of the fracture (flatfoot, pseudarthrosis). Only after the advent of Lauge-Hansen's classification has it become possible to compare the results for patients with identical fractures. Only the group of supination-eversion fractures, Stage IV, contains so many patients that it can be subjected to statistical treatment. A statistical analysis of the results in this group shows that the frequency of roentgenographically demonstrable osteoarthritis is significantly higher in patients with medium than in those with good position of the fracture and still higher in patients with poor position of the fracture.

The same applies to the presence of unilateral flatfoot following malleolar fracture and to rheumatic pain in relation to changes in the weather.[5]

On the other hand, the case material does not prove statistically that pseudarthrosis of the medial malleolus should exert any influence on the end-result.

8. Conclusions

The use of Lauge-Hansen's methods of genetic reduction has led to a considerable improvement in the results obtained in the treatment of fractures of the ankle in Denmark. As far as the severest forms of ankle fractures are concerned, Lauge-Hansen's methods gave a good result in almost twice as large a percentage as was obtained in an adequate control series (70% and 42%, respectively). Lauge-Hansen's technique gave also better results in the less severe forms of ankle fractures, but as the possibility of a definite improvement of the position is greatest in the presence of a markedly displaced fracture, the difference between the results in the latter group and those in the control series was not so great as in the former. Some of the poor results which were seen in the Lauge-Hansen series were due to secondary displacement which occurred because a new plaster cast had not always been applied when the first became too large. Shortage of plaster of Paris due to war conditions was partially responsible for this calamity. For the same reason, reduction was sometimes postponed for a few days until the swelling had practically subsided in order to reduce the consumption of plaster. It is likely that an even higher proportion of good results might have been obtained if the fractures had been reduced immediately after the accidents. Thus, the results of Lauge-Hansen's method of reduction reported here are not an expression of the maximum efficiency of the technique, but nevertheless they show distinctly that his method are superior to those previously used in this country.

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A New Device for Operative Intubation of Cecum and Other Hollow Viscera

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and
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The operative introduction of a tube into the colon, usually the cecum, in the surgical management of intestinal obstruction or as a complementary procedure after resection often requires cumbersome manipulation. Incision into the bowel wall may lead to spillage before the tube is introduced, even when protected by rubber-shod clamps. The use of a trocar and cannula followed by threading of a catheter through the cannula or by direct insertion of the catheter after the cannula is removed entails awkward maneuvering and invites the hazard of gross contamination.

The device herein described was planned in order to permit the direct introduction of a tube into the colon with ease and safety. The same instrument is also suitable for intubation of any hollow viscus or body cavity (e.g., closed tube drainage of the thorax).

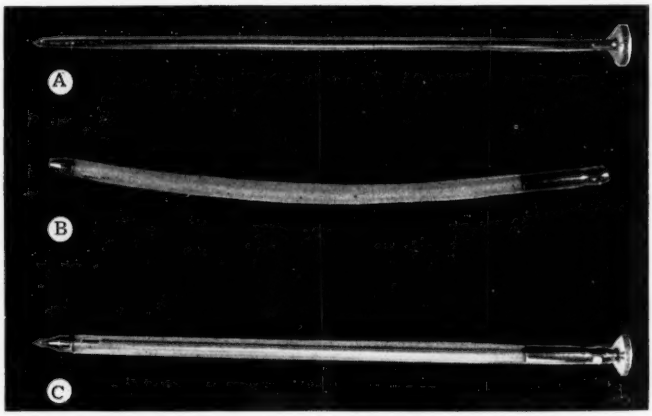

Fig. 1.—*A*, the trocar. *B*, tube with trocar removed. *C*, the instrument assembled for use.

Description

The instrument consists of a catheter containing a removable obturator with a sharp end (Fig. 1). The catheter is made of soft polyvinyl plastic material and has an auxiliary side opening near the distal end. The size illustrated is No. 28 F., but any size may be used. On each end of the catheter is a metal cuff. The obturator is a narrow metal rod whose distal end is a three-sided cutting point. The proximal end of the rod locks into the metal cuff of the tube.

When the device is assembled it is rigid. The obturator protrudes beyond the distal end of the catheter like a sharp trocar and easily penetrates the bowel wall. Once the end has entered the organ, the obturator is withdrawn, leaving the tube in place. Since the metal cuffs at the ends of the

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From the Surgical Service of The Mount Sinai Hospital.

Instrument manufactured by E. Miltenberg, Inc., 43 Great Jones St., New York.

polyvinyl tube are standardized to fit the obturator, the same obturator can be used many times over for different tubes of the same size. The tubes may therefore be discarded after several uses. A purse-string suture can be placed before or after the intubation, and the tube offers the same resistance to occlusion by the purse-string suture as does the usually employed rubber catheter. We have found that the bowel wall tends to grasp the tube so that no spillage of intestinal contents occurs during the introduction, thus facilitating placement of the suture.

An optional modification of this instrument is the inclusion of a side-arm extension of the proximal metallic cuff. This permits immediate suction decompression of intestinal content without the necessity for clamping the end of the tube (Fig. 2). After suctioning is completed, the side arm of the tube is removable.

Comment

This trocar-tube has been successfully used several times for a complementary tube cecostomy after colon resection (when the cecum was collapsed) and also for a decompressive tube cecostomy in the treatment of acute intestinal obstruction (when the cecum was markedly dilated and thin-walled). In both sets of circumstances introduction was simple and no spillage occurred. Wherever the intestinal tract (small or large bowel) requires operative intubation for decompression, this device, in appropriate size, is applicable.

The instrument has also been introduced into the pleural cavity without difficulty in an acute traumatic tension pneumothorax after a small stab intercostal incision has first been made. This procedure is also advantageous for underwater closed drainage of empyema fluid.

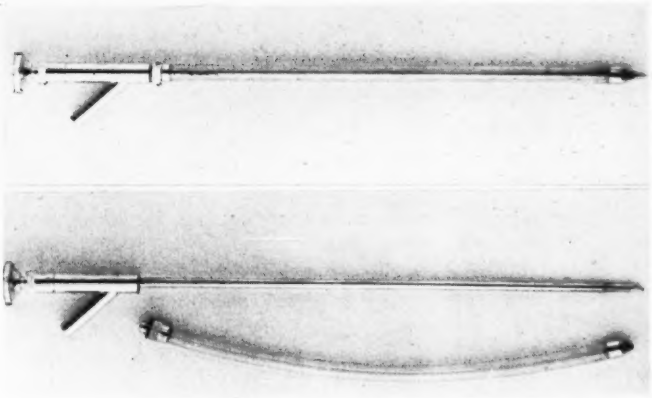

Fig. 2.—Modified instrument with removable side arm for suction.

Experiences with More Than One Thousand Elderly Surgical Patients

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The results of major surgery have improved enormously in the past 20 years. Not only is surgery now safe for the patient but we are learning something of how to make the patient safe for surgery. As a result, major operations can be carried out at ages, both young and old, which were previously thought to be an absolute barrier.

At the same time, with the increased expectation of life common to all civilized countries, the surgery of the elderly patient is becoming increasingly important. In Great Britain, life expectancy at birth for men has increased from 48.5 years in 1900 to 66.3 years in 1950. At the age of 60, life expectancy is 74.8; at 70, it is 79. Moreover, between 1931 and 1951, while the total population of the country increased by 8%, the number of persons more than 70 years of age increased by 72%. Trends in Western Europe are similar. It is therefore important for both practitioner and surgeon to know what can be expected of surgery for those of advancing years. Is surgery to be merely palliative, to be recommended only as a last resort, or can we undertake major operations with reasonable chance of success?

At the outset of any consideration of geriatrics, the question of a lower age limit must be settled. For obvious reasons this decision must be arbitrary. Cole (1953), after an extensive survey of the literature, considers that 60 years should be set as the lower limit, as do Estes (1949), Cutler (1950), and Haug and Dale (1952). Ziffren (1953), on the other hand, reviews the results of his cases above the age of 80. In view of the increased expectation of life of the present generation, it appears to me, as also to Nissen (1953), that the special considerations inherent in the surgery of old age may be most fairly presented in those above the age of 70.

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Schaerbeek Hospital.

Present Series

The present series covers the 1136 patients more than 70 (12.8% of the total number of inpatients) admitted to the general surgical wards of Schaerbeek Hospital, Brussels, between 1945 and 1953. Urological, ophthalmic, and ear, nose, and throat cases are excluded, being under special departments. All other cases are included, whatever their condition on admission. Ages ranged from 70 to 93, the average being 76.1 years.

Schaerbeek, one of the main suburbs of Brussels, is a middle- and working-class district. There is no shortage of hospital beds, and with the health insurance scheme patients have free choice of physician and hospital. Home nursing facilities, on the other hand, are on the whole lacking, whereas "hospices" for the aged and infirm are crowded and admission is difficult. In consequence, elderly patients tend to stay in the hospital, and the follow-up presents no difficulty.

The commonest causes for admission were trauma (including burns) and cancer, which together were responsible for more than half the admissions. Infections, herniae, arterial and venous thromboses, aneurysms, reticuloses, and surgical conditions of the

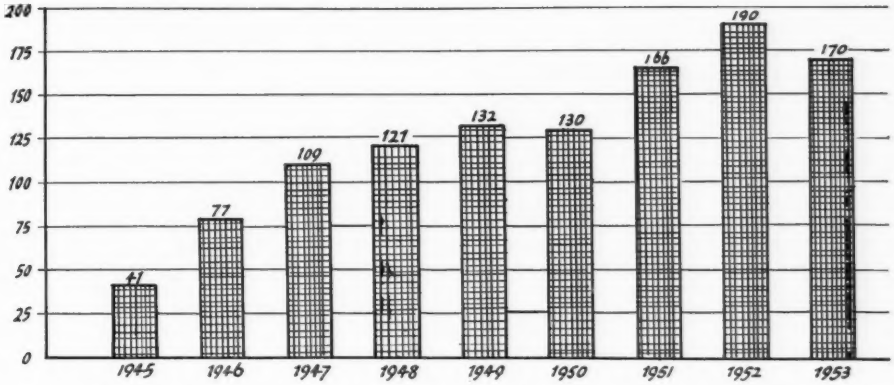

Fig. 1.—Yearly admissions of surgical cases more than 70 years of age (1945-1953).

skin and of the nervous and endocrine systems accounted for a further third. Cancer leads as the cause of death, being responsible for 103, or more than one-third of all the deaths in the series. Many of these cases were admitted in hopelessly advanced condition, which is reflected in the very high cancer mortality rate. Trauma proved a close second and was responsible for 93, or 32%, of the total number of deaths. Severe multiple injuries following road accidents, chest injuries, and fractures of the skull and of the femur were largely responsible.

TABLE 1.—*Diagnoses and Mortality of 1136 Consecutive Cases More than Seventy Years of Age (1945-1953)*

	Number	Per Cent of Admissions	Deaths	Per Cent of Mortality
Trauma and burns	469	41.2	93	19.8
Cancer	182	16	103	56.5
Acute abdominal conditions (not cancer or hemorrhage)	81	7.1	23	28.3
Intestinal hemorrhage	29	2.5	9	31
Infections and miscellaneous	375	33	62	16.5
Total	1136	----	290	25.5

Of the whole series, 167, or 1 in 7, were found to show clinical evidence of cardiovascular disease. Sixty-four, or 38.3%, of these cases died, as against an over-all mortality for the whole series of 25.5%. The high mortality rates of acute abdominal conditions (28.3%) and of intestinal hemorrhage (31%) are noteworthy.

The number of elderly patients admitted for trauma in the present series and the fact that one in five of the victims died show how much remains to be done in the prevention of accidents on the road and in the home.

Extensive burns in elderly persons are a very formidable problem. The same basic principles of treatment apply to all ages, but it is believed that these patients should be treated in special units.

The mortality after fractures of the upper limbs proved strikingly less than that following fracture of the lower limbs. Fractures of the neck and shaft of the femur remain serious injuries in old people. Every effort should be made toward early rising and ambulation. When the patient is perforce confined to bed for a long time, good nursing is all-important. Provided that the patient is cooperative and carries out regular breathing and limb exercises, it is often surprising how well prolonged immobilization is tolerated.

The outlook for the chronic bronchitic has been greatly improved since the advent of the antibiotics, and the mortality from pulmonary infections during the years of the

present series has been much reduced. Infective pericarditis is not easily diagnosed and may be overlooked; its presence should be suspected when heart failure supervenes in a patient suffering from a severe infection.

The results of treatment of arterial thrombosis have been disappointing. In acute thrombosis surgical measures have proved unsuccessful and I have reverted to anticoagulant therapy alone. In cases of long duration in which the obstruction is well localized, endarteriectomy has proved valuable. In thrombophlebitis, on the other hand, anticoagulant therapy has given consistently satisfactory results, causing rapid improvement and much shortening of the course of the disease.

Results of Surgery in the Present Series

Four hundred eighty-one operations were performed in the whole series. Of these, 145 were minor in nature and were without mortality; 336 were major, including surgery of the skull, head and neck, thyroid, breast, chest wall, limbs, and all abdominal and major gynecological operations. Of the 336 cases undergoing major surgery, 69 died within 30 days of operation and are therefore considered to be postoperative deaths, representing a mortality of 20.5%.

TABLE 2.—*Operations and Mortality*

	Number	Deaths	Mortality
Minor operations	145	0	0
Major operations	336	69	20.5%
Total number	481	69	14.3%

TABLE 3.—*Major Operations: Type of Operation and Mortality*

	Number	Deaths	Mortality
Planned operations	234	39	16.6%
Abdominal emergencies	48	19	39.5%
Strangulated external herniae	47	9	19.1%
Other emergencies	7	2	28.5%
Total number	336	69	20.5%

Planned Operations

The results of planned surgery in the present series show that the mortality rate, although definitely higher than in the younger age groups, is not prohibitive (16.6%). Among the operations carried out were block dissection of the neck, thyroidectomy, radical amputation of the breast, gastrectomy, cholecystectomy and choledochotomy, anterior colectomy, abdominoperineal and perineal excision of the rectum, Wertheim's hysterectomy, major amputations of the limbs, pinning of the neck, and open reduction and nailing of the shaft of the femur.

Gastrectomy for chronic peptic ulcer gave most gratifying results, chronic invalids being restored to health and activity. Pyloric stenosis was treated whenever possible by partial gastrectomy. Gastroenterostomy is certainly a less serious operative undertaking, but delay in function of the stoma has proved troublesome in long-standing cases.

On the other hand, cholecystectomy and exploration of the common bile duct, even with normal liver function, proved a serious operation in the present series (18 cases with 3 deaths, as compared with a personal series below 70 years of age of 300 cases with one death). Cholecystostomy was well tolerated and proved life-saving in cases of purulent cholecystitis, including patients more than 80 years of age.

Even the most extensive operations can sometimes be successful in these advancing years.

A woman aged 78 was admitted to the hospital for a spontaneous fracture of the upper end of the femur through a fibrosarcoma the size of a football. She was in intolerable pain from the lesion but otherwise fit and without evidence of metastasis. After due preparation, a hindquarter amputation was performed, the patient receiving a total of 4260 ml. of fluid intravenously during operation (blood, plasma, and hydrolyzed dextran [Macrodex]). Her anesthetic chart (Fig. 2) shows the changes in blood pressure during operation, the salient point being that at no time was it allowed to fall below 120/70. She was up on her 14th postoperative day and made an uninterrupted recovery. The photograph shows her condition two weeks after operation.

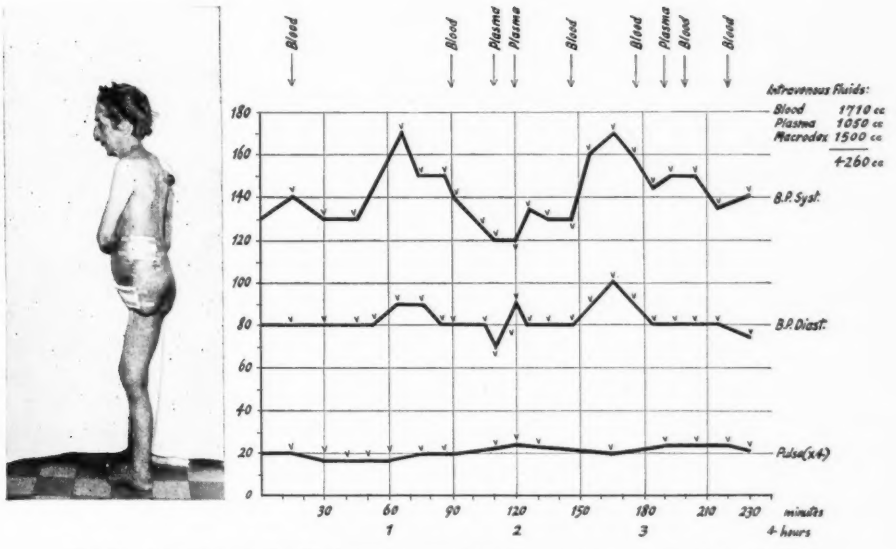

Fig. 2.—Woman aged 78. Hindquarter amputation for massive sarcoma of the thigh. Anesthetic chart and photograph on the 14th day after operation.

Emergency Operations

Emergency abdominal operations were for acute cholecystitis, perforation, appendicitis, diverticulitis (all with peritonitis), intestinal obstruction, and strangulated hernia. Many of the cases of peritonitis and intestinal obstruction were admitted late in the course of the disease, their poor or hopeless condition being due to delay. Even emergency transverse colostomy for sigmoid obstruction carried a high mortality, in spite of full preoperative treatment. All but two of the cases of appendicitis had either an abscess or generalized peritonitis, whereas 14% of the strangulated herniae required resection. We believe that had they been seen in the early stages of the disease, before the onset of irreversible water, protein, and electrolyte changes, many deaths could have been averted. The following pairs of cases are illustrative.

A woman of 78 years was seen 48 hours after the onset of acute small-bowel obstruction. A diagnosis of gallstone obstruction was made, the stone being felt per vaginam. A straight x-ray of the abdomen showed the stone. It was removed at laparotomy, and the patient made an uneventful recovery.

A woman of 76 years who was known to have a large gallstone was sent to the hospital five days after "another attack of biliary colic." On admission she had complete obstruction and was in advanced circulatory failure. After reanimation, the stone was easily found at operation but the bowel was gangrenous. She died on the 4th postoperative day.

A man of 70 years was admitted with a volvulus of the sigmoid colon of 48 hours' duration. The bowel was resected and a double-barrelled colostomy performed. Convalescence was smooth and the colostomy was later successfully closed.

A woman of 83 years was admitted with a volvulus of the sigmoid colon of six days' duration. At operation the whole loop was found to be gangrenous down to the upper part of the rectum. Resection was performed (Hartmann's operation) but she died on the following day.

On the other hand, the present series includes strangulated herniae with gangrenous bowel successfully resected in patients aged 84, 86, and 87, whereas we have many times been impressed by the smooth convalescence of elderly patients who have undergone operations for serious abdominal emergencies, provided that the diagnosis is made and treatment instituted in the early stages of the disease. The following two cases are given as examples.

A man of 79 had an acute small-bowel obstruction caused by a band at the site of a previous appendectomy. Operation 12 hours after his first symptom was followed by an uneventful recovery.

A man of 77 had a perforated duodenal ulcer. Simple closure was carried out five hours after the onset. Convalescence was smooth, without complication of any kind.

Hematemesis and Melena.—In advancing years these present a notoriously difficult problem. In the present series 31% of these complications proved fatal. In our experience when an elderly patient bleeds from a known ulcer he has a better chance of survival with partial gastrectomy than with conservative measures. The following case shows some of the difficulties which have to be faced.

A man of 76 years had a sudden severe hematemesis and melena. He gave no history of former digestive complaint and showed no signs of cirrhosis of the liver. The spleen was not palpable. He was treated by blood transfusion and was maintained well compensated. He later developed a sudden epigastric pain and collapsed, without evidence of further hemorrhage. An electrocardiogram showed a myocardial infarct. At postmortem examination acute multiple ulcers of the stomach and duodenum were found, together with a perforation of the heart from a large myocardial infarct.

Comment

The literature of geriatric surgery is sparse. Lack of uniformity in the lower age limit, the inclusion or exclusion of minor operations, and the absence of clear distinction between planned and emergency surgical procedures render the comparison of figures unreliable.

TABLE 4.—*Comparison of Figures of Operative Mortality in Elderly Patients*

Author	Number of Patients	Age, Yr.	Mortality Rates, %
Estes (1949)	400	More than 60	6.5 (14% minor operations)
Bosch and others (1952)	500	More than 60	9.6
Haug & Dale (1952)	354	More than 60	9
Cole (1953)	3,656	More than 60	5.1
Carp (1954)	938	More than 60	16
Nissen (1953)	231	More than 70	10
Limbosch (1955)	481	More than 70	14.3
Ziffren (1953)	429	More than 80	15.1

A number of articles concern personal series of operations with surprisingly good results, tending to suggest that surgical disease in the elderly is little more serious than in earlier years. Such results obviously reward a high degree of surgical skill and of selected cases they may well be representative. Over the whole subject, however, they are misleading. Obviously operability in the borderline cases is purely a matter of opinion, and, if only the more favorable cases are included, results as far as figures are concerned will be greatly improved. The following cases are given as examples.

A woman of 72 years, in poor condition, had an ulcer crater 1 in. deep on the middle of the lesser curvature of the stomach. Three surgeons had refused to operate, considering the case to be an inoperable carcinoma of the stomach. A subtotal gastrectomy was performed in the present series, and the patient made an uncomplicated recovery. Histological examination of the specimen showed a benign ulcer, penetrating the pancreas, on the edge of which a small nodule proved to be a lymphosarcoma. The patient died three years later of generalized lymphosarcoma.

A man of 87 years, still fit and active, had a large inguinoscrotal hernia which had bothered him for years and had recently endangered his life with recurrent obstruction. He had been repeatedly advised to wear a truss, without improvement. Operation was performed (lattice repair with nylon) and was followed by an uncomplicated recovery.

In the present consecutive series, including all cases admitted to the hospital during nine years, the over-all mortality (25.5%) is high. Apart from special social factors outlined above, undoubtedly the greatest factor in this high mortality was late diagnosis and late admission to the hospital. None the less, our experience confirms that of others, that even the most extensive operations can be successfully carried out on patients of advancing years. Cattell (1947) reported a successful right hemicolectomy in a patient of 93; Nissen (1953) reported a successful esophagogastrectomy in a patient of 81, whereas the present series includes a woman of

78 who survived a hindquarter amputation.

It has been repeatedly stated that aged patients stand emergency operations badly. Cutler (1950) reported a mortality of 53% for acute intestinal obstruction in patients more than 60. Carp (1954) had a mortality rate for emergency surgery in patients more than 60 years of age of 53.8% and of 32% in two large series, from 1939 to 1945 and from 1945 to 1951, respectively. The figure of 39.5 mortality for abdominal emergencies in the present series would appear to bear this out. On the other hand, provided that there had been no delay in diagnosis or treatment, the smooth convalescence of many of our cases was impressive.

According to our data, it is more correct to say that elderly patients, with their diminished adaptability to strain, stand delayed treatment badly. We suggest that a lowering of this high mortality rate is as much a medicosocial problem as a surgical one and that it can be summarized in four words—early diagnosis and treatment.

Consideration of Surgical Risks

The mortality rate for major operations in elderly patients is, and always will be, higher than in younger patients. The very fact of senescence implies a diminished adaptability to stress. Cole (1953) sums up the position aptly in saying that "if concurrent and complicating disease can be eliminated, aged people will tolerate operations of moderate magnitude almost as well as young people." Any complication, however, added to the load of operation may turn the scales against the patient. The following case is an example.

An obese woman of 86 years had a large strangulated inguinal hernia containing 3 ft. of gangrenous bowel. Her general condition, however, was good, and she stood her operation well. She was out of bed on the following morning, and on the third day bowel sounds were good. On the evening of that day, she suddenly ran a high temperature, became dyspneic, and went rapidly into coma. Examination revealed an atelectasis of the base of the right lung. She died shortly afterward, and necropsy showed a comparatively small collapse of the base of the right lung, the anastomosis and the abdomen being entirely sound. The pulmonary complication was too much for her.

Shock.—It is well known that elderly people stand shock and hemorrhage badly. The senile vascular system and kidneys are unable to withstand major variations in blood pressure or volume. Beling and coworkers (1952) stress this point and make particular mention of patients suffering from malignant disease, whose blood volume may be considerably reduced. Prevention rather than treatment is the key to the situation if irreversible damage is to be averted.

Obviously one of the most important factors is surgical technique. Extreme gentleness, bloodless dissection, and accurate and careful suturing, in order to inflict the least trauma, are essential. As Rowntree said, "an hour of gentleness is safer than 10 minutes trauma." In no branch of surgery is this more relevant.

Good anesthesia is essential. Only a skilful anesthetist can combine light general anesthesia with the absolute muscular relaxation necessary for careful, atraumatic surgery. Constant observation of the blood pressure and the careful supervision of intravenous infusions during operation are also carried out by him.

Fluid and Electrolyte Balance.—Perhaps the most difficult problem in the management of the elderly surgical patient is the pre- and postoperative correction of disturbances of water, electrolyte, and protein metabolism. As many of the cases in the present series came to surgery late in the course of their disease, preoperative assessment of their condition was by no means easy. In certain cases it was believed that the cardiovascular system would be unable to deal with the large quantities of fluids required. Such cases could be treated only by the method of trial and error, by estimating the amount of fluids and electrolytes to be given in perhaps four hours, and by observing the patient's reactions to treatment at the end of this time. In some of

our cases irreversible renal damage was already present. The following case is an example.

A woman of 84 years had a strangulated femoral hernia of many days' duration. She had a gross deficit of fluids and electrolytes. In spite of full replacement therapy and without further losses, renal failure with steadily rising blood urea set in after the operation and she died without other obvious complications on the sixth postoperative day.

Plasma has been used exclusively in replacement therapy in the present series, with a view to maintaining the circulating blood volume, and has given good results.

A man of 76 years developed a severe paralytic ileus after operation for acute appendicitis with general peritonitis. He received daily 3 pt. of plasma in his calculated requirements intravenously, together with volume-for-volume replacement of fluid aspirated. His ileus lasted six days, but thereafter he made an uninterrupted recovery without renal or circulatory complication.

Cardiovascular Complications.—Cardiovascular accident as a cause of death in younger patients is, in our experience, rare. It is by no means so in patients more than 70. The present series shows the incidence of cardiovascular disease in elderly surgical patients and indicates that the death rate in such patients is definitely raised.

A woman of 76 years suffering from a carcinoma of the uterus had marked pulmonary emphysema. Before operation she was well compensated. After a total hysterectomy she developed a progressive right heart failure and died on the ninth postoperative day, in spite of full supportive measures.

Preoperative assessment of such patients is always difficult. Functional tests and the electrocardiograph may be of help, as in the following case.

A man of 72 years had two years previously had a perforation of a duodenal ulcer treated by simple suture. He subsequently developed pyloric stenosis and became almost completely obstructed. He was considered a poor operative risk on account of permanent arrhythmia of the heart. An electrocardiograph showed a "wandering pace-maker." Partial gastrectomy was performed and convalescence was smooth.

Pulmonary Complications.—In the present series postoperative pulmonary complications were not formidable as described by other writers. Haug and Dale (1952), for instance, found pulmonary complications to be the most frequent postoperative incident (24.6% of all complications). We believe that this may be due, at least in part, to our routine use of antibiotics both before and after operation. The sensitivity of the organisms in the sputum was routinely tested, and suitable antibiotics were used.

Pulmonary embolism similarly ranks high in the list of postoperative complications in elderly patients. Bosch and associates (1952) report a death rate of 10%, Carp (1954) 7%, and Haug and Dale (1952) 16%. The death rate from pulmonary embolism in the present series was 5.8%. This improvement may be due to our routine use of anticoagulants. Forty-eight hours after operation, ethyl biocoumacetate (Tromexan) was given routinely in amounts sufficient to keep the prothrombin time between 10% and 20% of normal. Heparin was used only if oral administration was impossible. This therapy was continued until the patient was fully active.

Early ambulation alone does not prevent fatal accidents from pulmonary embolism.

A woman of 72 years developed a general peritonitis from perforation of a diverticulitis of the sigmoid colon. Mobilization and exteriorization of the diseased bowel was carried out, with drainage. The patient was immediately ambulant but dropped dead on the 11th postoperative day. The postmortem examination showed massive pulmonary embolism, the clot originating from the left iliac vein.

Wound Disruption.—This is a serious postoperative complication in the elderly patient. In the present series it occurred only twice. We believe that this was due to two factors: (1) avoidance, as far as possible, of long midline incisions and (2) routine closure of abdominal wounds with interrupted nonabsorbable sutures for each layer. Since nylon became available, shortly after the war, we have used it exclusively.

Unexplained Deaths

Apart from these recognized complications, deaths whose exact cause is problematical occur in elderly patients.

The following case illustrates this fact.

An old man had a leg amputated for arteriosclerotic gangrene. He stood his operation well but died five days later without obvious complication; clinical, laboratory, and post mortem-room findings failed to show any obvious cause of death.

Similarly an elderly woman was admitted with a fractured neck of the femur; this was duly nailed in good position, but she never recovered her interest in life and faded away without obvious complication.

The use of corticotropin (ACTH) in such cases has recently attracted attention. Cole (1953) reports the case of a man aged 71 in very poor condition upon whom he was able, with the aid of corticotropin, to carry out a successful pneumonectomy. In the latter part of the present series corticotropin in cautious doses has on several occasions caused a dramatic improvement in the postoperative condition of elderly patients who were failing to progress in their convalescence.

A man of 84 years had a strangulated inguinal hernia. After operation, he developed retention of urine, for which he eventually had an endoscopic resection of the prostate on the 12th day after his original operation. In spite of apparently normal renal function and without evidence of cardiovascular complication, his condition remained poor. He had no appetite and no energy. After three days' treatment with corticotropin his appetite had improved enormously and he was almost fully active. Recovery was complete.

Conclusions

The defeatist attitude toward geriatric surgery common among physicians and the general public is unjustified and should be dispelled. The results of surgery in old age can be gratifying, and necessary surgery should not be withheld on the score of age alone.

Much remains to be done in the prevention of trauma in old people and in stressing the disastrous results of delay in diagnosis of both malignant disease and acute abdominal conditions. Early diagnosis and treatment are every whit as important as in younger patients.

For the surgeon emphasis must be laid on the prevention of complications. Above all shock must be averted by careful supportive measures, by good anesthesia, and by careful, atraumatic surgery.

Given these, the outlook for the elderly surgical patient is encouraging.

Summary

With the present-day steady increase in the general expectation of life, geriatric surgery is assuming an increasingly important role. Toward the evaluation of that role, a series of 1136 consecutive surgical cases more than 70 years of age is reported. The over-all mortality in this series was 25.5%. No selection of any kind was involved, however, and many of the cases came to treatment tragically late in the course of their disease.

The series shows that even in old age major operations, both planned and emergency, can be undertaken with good hope of success, provided that complications of any kind are averted. The greatest individual factor is early diagnosis and treatment. Of almost equal importance is the avoidance of shock by careful preparation, adequate supportive measures, good anesthesia, and careful surgery.

Neither pulmonary nor thromboembolic complications proved as frequent as in other published series, possibly owing to the routine use of correct antibiotics and of anticoagulants. Abdominal wound complications have been diminished, we believe, by the use of oblique or transverse abdominal incisions where possible and by closure of the wounds with interrupted nonabsorbable sutures.

Attention has been drawn to the value of plasma in intravenous therapy in the postoperative period, whereas recently corticotropin (ACTH) has been used effectively and even dramatically in improving the general condition of debilitated elderly patients.

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Complications from the Use of Absorbable Hemostatic Sponges

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Review of the Literature

Since 1942 a large body of literature has grown around the use of the three types of absorbable hemostatic sponges which are now widely recommended and are the subject of this study: those made of fibrin (Fibrin Foam, Zimospuma); oxidized cellulose (Oxycel, Hemo-Pak, Zellurongaze), and gelatin (Gelfoam, Spongostan, Spongioprot, Topostasin). In 1945 Jenkins and Clark [1] cautioned against the indiscriminate use of these materials. Frantz and associates [2] suggested in 1944 that oxidized cellulose be used "in as small quantity as possible." However, in 1946 Frantz [3] stated in a critical review of all three types of hemostatic sponges that there is no evidence of unfortunate late sequelae, and "they are all apparently safe and useful." The great majority of writers have emphasized the minimal tissue reaction, the rapid absorption, and the good hemostatic properties of these agents; in a review of the literature I found 130 papers, based on experimental or clinical data, or both, which testify to the advantages of these materials without mentioning complications from their use. One gains the impression that it is now rather common practice to cover wound surfaces freely with these three types of sponges and to pack them unhesitantly into various large and small postoperative cavities.

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From the Department of Surgery, University of Utah School of Medicine. The experimental studies are from the Addison H. Gibson Laboratory, University of Pittsburgh. Most of the clinical material is from the Surgical Service, Veterans Administration Hospitals, Pittsburgh.

Conflicting Observations About Absorbable Sponges Accumulated in the Literature

The absorption time of the hemostatic sponges implanted in living tissue has been estimated by most writers to be between three and four weeks for all three types referred to here. With respect to fibrin foam, an absorption time of more than 100 days [4] has been listed. Unabsorbed gelatin sponges have been found to remain in wounds 2 months,[5] and even 12 months,[6] after implantation. Some authors were not impressed with the absorbable property of oxidized cellulose.[7]

The great majority of the clinical and experimental studies have led to the conclusion that there is insignificant or no tissue reaction to these hemostatic agents. In a few of the publications one can, however, see microphotographs with broad margins of granulation tissue surrounding sponge rests, and also find unfavorable comments. Lang [8] described a "sharply demarcated granuloma with a small piece of Fibrin Foam in its center" 60 days after implantation of bovine fibrin. Use of gelatin sponge has led to "large areas of connective tissue,"[9] "excessive fibrosis," and autolysis of tendon grafts[10]; a more or less intense cellular infiltration [11] and active fibroblastic proliferation in one out of four clinical cases was also described.[12] Busch and associates [13] stated that gelatin film is unsuitable as a substitute for the dura mater because of the broad adhesions it formed with the brain. Blaine [14] showed the liver of dogs to be partly fibrotic and necrotic 28 days following implantation of gelatin

sponge. In this connection it is of interest to note that gelatin has been placed in wounds for the specific purpose of promoting growth of granulation tissue and local pleural adhesions. Oxidized cellulose has been found to cause fibroblastic reaction of peritoneum and adhesions between omentum and peritoneum,[15] and to give an inflammatory effect on brain tissue.[16] In 15 out of 53 operations on man by Buchman and Blair[17] complications from irritations by hemostatic sponges resulted in some delay of wound healing; they abandoned "the use of Oxycel and Gelfoam as fillers for bone cavities."

The advocates of absorbable hemostatics, with very few exceptions, have not mentioned that an infected or potentially infected field would be a contraindication; several authors specifically recommend the sponges even under such circumstances. On the other hand, a few authors have stressed that hemostatic sponges may have a deleterious effect on the healing because of increased danger of infection. In some animal experiments all three types of sponges were found to intensify infection;[18] in others, gelatin and oxidized cellulose led "almost constantly" to abscesses in infected nephrectomy wounds.[19] Increased incidence of perforation and peritonitis in bowel surgery was observed after application of gelatin and oxidized cellulose,[20] gelatin sponge,[21] and oxidized cellulose.[22] Previous conclusions that absorbable hemostatics are easily and rapidly absorbed in nephrectomy wounds of animals do not apply to clinical urology according to Hinman and Babcock.[19]

There are also some clinical observations of postoperative infections following application of absorbable hemostatic sponges in the otherwise very favorable literature on this subject. Introduction of gelatin sponge in 28 postextraction cavities[23] and in chest wound[24] led to septic sockets and drainage respectively. Kravitz and Breed[25] give a thorough report of an abdominal abscess around a gelatin pack. Oxidized cellulose has caused delayed healing of oral cavities[26] and of nasal mucosa (Elsbach[27] and others). This substance has reportedly led to infection or necrosis in the gallbladder bed (Vanderhoof and associates[28] and others), to peritonitis,[29] to urethral obstruction,[30] and to fatal intestinal obstruction.[31] Studdiford[32] discusses the certainty of bacterial infection when the uterus is packed with absorbable gauze by the vaginal route.

It seems that these adverse data on the use of hemostatic sponges have faded so much against the main background of favorable reports that it is only when they are compiled that they take on a real significance.

Experimental Studies

In three rabbits and seven dogs absorbable hemostatic sponges were implanted subcutaneously in craniotomy wounds under sterile precautions. On each animal bilateral craniotomies, measuring about 1×2 cm., were made through separate parasagittal incisions 3 cm. long. All bone chips were removed by thorough irrigation with saline solution. In 6 of the 20 craniotomies the dura was covered with oxidized cellulose; a two-layer pad was applied in three of the wounds, and a thicker pad of six layers was inserted into each of three other craniotomies. In 12 craniotomies a piece of gelatin sponge, cut from the regular-size 6-mm.-thick gelatin sheaths to fit the skull openings, was placed over the exposed dura. Two craniotomies were used as controls. Fresh blood was allowed to be absorbed by the sponges. The wounds were not closed until bleeding had stopped. No bone wax or other foreign body besides the sponges and the skin sutures was introduced into the wounds, which were closed with fine silk and then covered with tincture of benzoin and collodion; the sutures were removed in five days. All of these animals except two received 100,000 units of penicillin daily, for the first three postoperative days.

No swelling or other signs of wound infection occurred except that in one dog, which had received penicillin postoperatively, a subcutaneous accumulation of fluid developed over the gelatin-packed craniotomy on one side. This was noticed the third postoperative day; the swelling disappeared after about 1.5 cc. of bloody fluid was aspirated. Unfortunately this fluid was not cultured; the following day when an at-

tempt was made to repeat the aspiration for culture, no fluid was obtained and no further swelling occurred. The penicillin injections were continued for five days in this dog, and the wound healed uneventfully.

The animals were brought to autopsy after having been given lethal doses of pentobarbital sodium (Nembutal) six to eight weeks postoperatively; histological sections were studied with use of various stains. In the cases where oxidized cellulose had been applied no remnants of it were found microscopically after six weeks, when only two layers were used. Of the six-layer pads, there remained at eight weeks a thin gelatinous mass, partially replaced with loose fibrous tissue; a light fibrous reaction was found on the outside of the dura where the oxidized cellulose had been

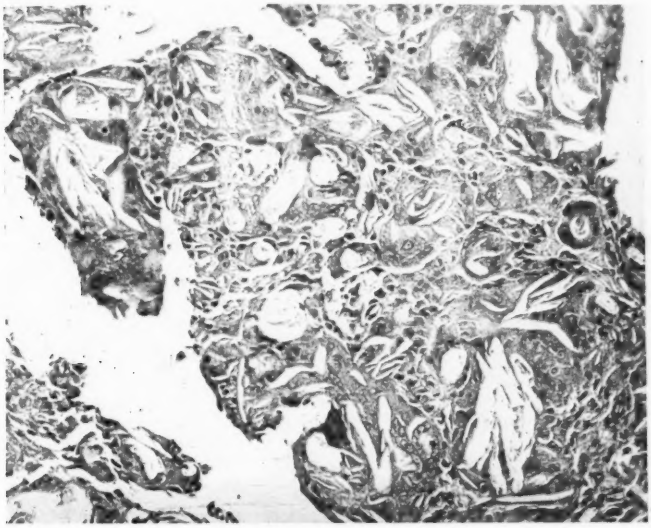

Fig. 1.—Foreign-body reaction about gelatin placed in craniotomy of dog, 6 weeks previously. Hematoxylin and eosin; reduced about 1/5 from mag. × 150.

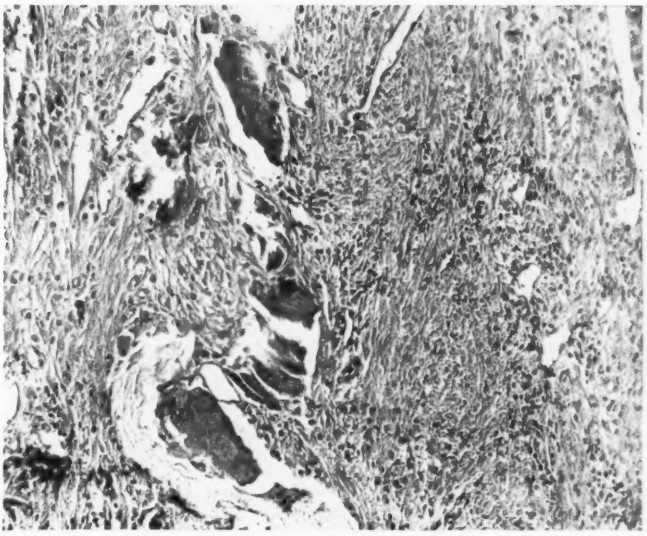

Fig. 2.—Gelatin fragments causing giant-cell formation and fibrous tissue proliferation, 8 weeks postoperatively.

placed, but no thick dural scar resulted.

The gelatin sponges had, after six to eight weeks, in most cases been resorbed and replaced by a layer of loose fibrous tissue. In some instances the fibrous proliferations were thicker or a foreign-body reaction was noted around microscopic rests of gelatin (Fig. 1). The dog that had developed the temporary subcutaneous fluid accumulation mentioned above showed in the craniotomy on that side a large pad of firm granulation tissue after eight weeks (Fig. 2); in the cranial defect over the opposite hemisphere there were even thicker granulations, although no postoperative swelling or clinical sign of infection had occurred there (Fig. 3). In another dog, killed after 8 weeks, one of the craniotomies was filled with a dense fibrous scar containing microscopic gelatin frag-

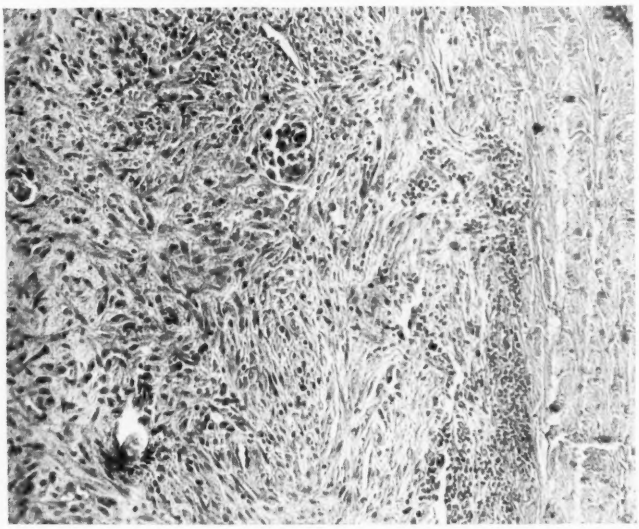

Fig. 3.—Dense extradural granulation tissue replacing gelatin, 8 weeks postoperatively.

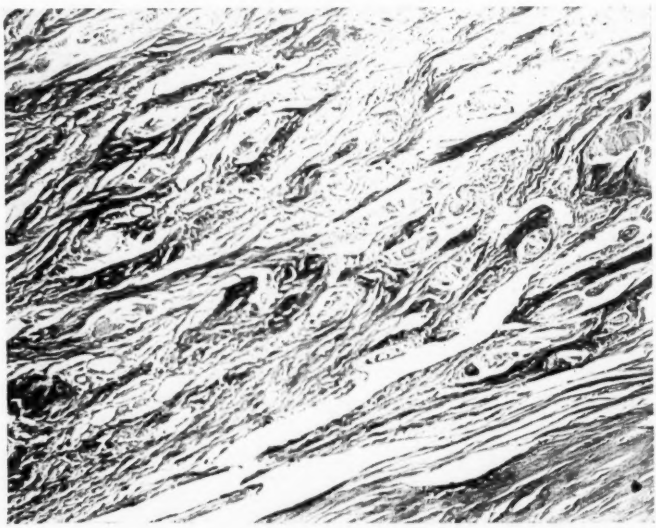

Fig. 4.—Thick extradural scar. Note fragments of gelatin, 8 weeks postoperatively.

ments (Fig. 4); the skull opening on the opposite side contained only a comparatively loose fibrous mass. The heavy irregular scars attached to the outer side of the thickened dura in these three particular craniotomies resemble the fibrous proliferation around muscle pieces implanted for hemostasis.

An attempt was made to ascertain whether the sponges contain enough air to promote growth of aerobic cultures. The centers of thick agar plates were inoculated with aerobic Staphylococcus albus and each one was covered by a 2×2 cm. sheath of gelatin sponge. The sponges were, in turn, covered by a thick layer of hardened agar that extended well over the edges of the sponge. To seal off the edges airtight liquid agar, which had been cooled to just above the solidification point, was poured over it. The petri dishes were kept in a low-oxygen atmosphere. Readings after 24 hours demonstrated an abundant growth of the aerobic cultures about the sponges. Controls, without the porous gelatin sponges between the layers of agar, showed less growth, and so did the same aerobic cultures when the gelatin sponges had been thoroughly compressed before they were placed between the agar slabs. The gelatin sponges may retain enough air bubbles to keep alive aerobic organisms which in the average closed wound would tend to die out.

The estimates of the absorption time of these hemostatic sponges have been shown to vary considerably among the many published studies. One explanation for this discrepancy is that experimental methods were far from standardized. Usually, the size of the animals, the amount of sponge deposited, and the extent of bleeding varied. There is, however, a difference in absorption rates in various tissue beds. A foreign-body reaction adjacent to bone and periosteum is more apt to produce thick fibrous scars and calcification than a similar granulation in subcutaneous tissue. It seems, however, that the variations in absorption time and tissue reaction have not been generally recognized.

Where an excessive tissue reaction to absorbable hemostatics has been found, mild secondary infection rather than the irritation from the sponges has probably been responsible for the fibrous proliferation and the adhesions. Not only are these hemostatic sponges (except for cellulose) culture media themselves, but the blood they absorb or cover is not so readily reached by antibiotics or removed by phagocytosis as when the clot is directly surrounded by viable tissue. If hemostatic bodies not only were tissue-friendly but also were absorbed in a few days or hours, the risks of late complications would decrease.

Clinical Observations

The following three case histories illustrate the difficulty in controlling some infections where hemostatic sponges had been implanted:

Report of Cases

CASE 1.—A 30-year-old man had a cerebral arteriovenous aneurysm extending over the medial side of the left parietal lobe. On Feb. 18, 1953, it was resected, leaving a cup-shaped defect 4 cm. deep and 4 cm. wide, the walls of which were covered with four pieces of gelatin sponge, each measuring about 2 × 4 cm. Postoperatively the patient was given penicillin, 300,000 units, and streptomycin, 0.5 gm., twice daily. At first he seemed to do well. After four days he developed neck stiffness, headache, and slight fever; the spinal fluid, under 280 mm. pressure, showed 3400 white blood cells, of which 10% were lymphocytes. The doses of antibiotics were doubled. Five days later the spinal fluid was clear and the cells had decreased to 93. The patient felt and looked better; an arteriogram did not show the previous aneurysm. Three weeks postoperatively the antibiotic medication was discontinued. Twenty-four hours thereafter severe headaches, nausea, and malaise ensued, and the spinal fluid cells increased to 1600 white blood cells. At no time was there any growth on culture of the spinal fluid. On the 25th postoperative day the patient was reexplored and a suspected brain abscess was found, which in size and location corresponded to the outline of the original surgical defect. The pus contained remnants of absorbable gelatin sponge (Fig. 5). Bacterial stain revealed Gram-positive cocci and culture pro-

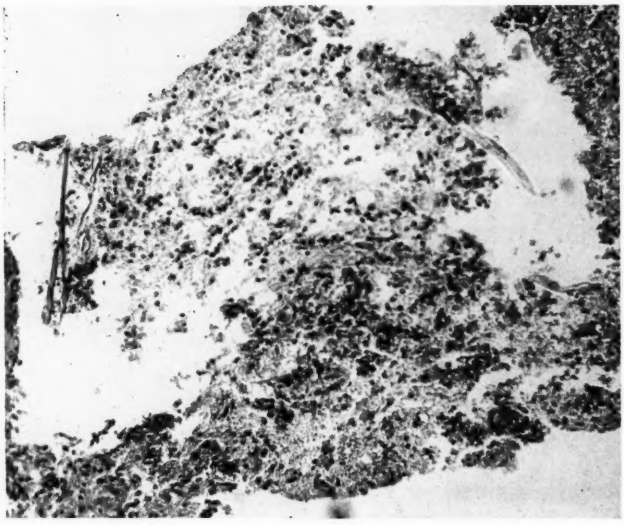

Fig. 5.—Intracerebral abscess around gelatin, 25 days after implantation of the hemostatic sponge.

duced Staphylococcus aureus which was sensitive to antibiotics other than penicillin, and the medication was changed accordingly. Ten days after the drainage of the abscess the patient was ambulatory, and shortly thereafter he was discharged, apparently free of cerebral symptoms except for right homonymous hemianopsia; he has remained so when last checked 23 months postoperatively.

Case 2.—A 42-year-old man, with headache and choked discs but in good general condition, was operated on Oct. 15, 1954, for a large left frontal lobe meningioma attached to the falx. Some bleeding points on the traumatized cortex were covered with gelatin sponges. A postoperative stupor slowly deepened and on the third day the flap was turned again, but a suspected postoperative hematoma was not found. The previously applied pieces of hemostatic sponges were removed. Extradural bleeding along the sagittal sinus in the anterior portion of the wound was controlled with three 2×6 cm. wide, regular strips of gelatin. After this second operation 0.5 gm. of streptomycin and 300,000 units of penicillin were administered intramuscularly twice a day, although there were no symptoms or signs of inflammation then. The stupor decreased somewhat but the patient remained dull and inactive, complaining of headache. Within a week he had developed a diffuse swelling of the forehead, and nine days after the first operation the anterior end of the incision opened, freely draining seropurulent material. Cultures showed Staph. aureus, sensitive to chloramphenicol (Chloromycetin) and erythromycin (Erythrocin) but not to penicillin or streptomycin; 250 mg. of chloramphenicol and 1 gm. of sulfisoxazole (Gantrisin) were given four times daily; the skin fistula was widened 3 cm. along the incision and found to open into a pus pocket around the most anterior burr hole, through which a rubber drain was inserted. In spite of this, the purulent flow and the swelling in the forehead did not decrease. The patient remained drowsy, slightly confused, and nauseated, and the frontal headache persisted. After another week, when the infected area was reexplored, the pus pocket was found to extend through the burr hole and to widen a few centimeters under the bone flap. This extradural abscess cavity contained partially disintegrated gelatin sponges loosely attached to the dura and infiltrated with bacterial colonies (Fig. 6). The purulent material including the gelatin was eliminated, and a drain was applied through the skin as before. The pocket of infection appeared fairly well walled-off. Culture of the pus yielded Staph. aureus of the same limited antibiotic sensitivity as before. Within 12 hours striking improvement occurred. Scant drainage continued for two weeks and then the fistula slowly closed. The significant feature was the dramatic clinical improvement and the prompt change from a profuse to a minimal purulent drainage as soon as the pus-soaked gelatin sponges had been removed. The wide wound opening and the large drain had seemed adequate for drainage, but no change for the better had taken place as long as the sponges remained in the wound. The spinal fluid did not show at any time, before or after the drainage of the abscess, any growth on culture or a higher cell count than 6 white blood cells or higher protein than 36 mg. per 100 cc.

Case 3.—A case from the files of Dr. Lars

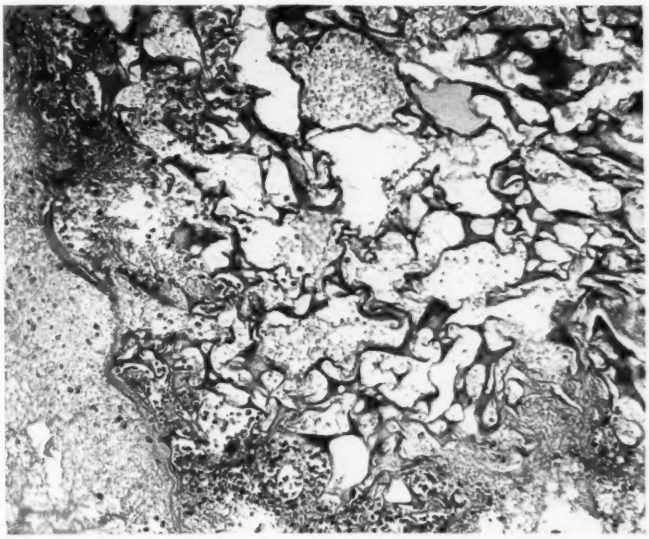

Fig. 6.—Extradural cerebral abscess around an absorbable sponge, 16 days after implantation.

Leksell, Chief of the Neurosurgical Clinic of the University of Lund, Sweden, is of interest in this connection*: A 60-year-old diabetic woman, in a state of depression, was suffering from severe thalamic pains secondary to a cerebrovascular accident. Through small burr holes over each prefrontal lobe a lobotomy was performed Dec. 15, 1952, by thermocoagulation within the white matter with use of a stereotactic apparatus. A gelatin sponge was placed over the cortex in the left cranial defect to obtain hemostatis. Postoperatively there was partial relief of pain, and in the first 12 days no complications were noted. Thereafter the patient appeared less alert and developed Jacksonian attacks on the right side. Since several postoperative electroencephalograms showed an epileptogenic focus over the left prefrontal area, the left craniotomy was reexplored two weeks postoperatively. No gross abscess was seen, but the gelatin sponges (Spongostan) that covered the cortex were removed and culture showed a growth of coagulase-positive Staph. albus. The cerebrospinal fluid was sterile. Following the removal of the contaminated gelatin the epileptic attacks ceased and the electroencephalographic cortical lesion could not be demonstrated in several new tracings. The patient became ambulatory and was discharged seven weeks after the lobotomy. An electroencephalogram taken four months thereafter failed to reveal any focal lesion. Dr. Leskell concluded that the secondary infection around the gelatin sponge placed over the cortex was most likely responsible for this epileptogenic focus.

* Dr. Leksell kindly granted permission to include this case in the present report.

Over a two-year period at the Veterans Administration Hospitals in Pittsburgh, we used gelatin sponges routinely to control epidural bleeding in 90 laminectomies for ruptured intervertebral discs. In three of these cases, postoperative purulent drainage with Staphylococcus aureus occurred. However, the sponges were not removed from the wounds, and it took three to five weeks before the drainage had ceased in spite of antibiotics. No conclusions could be drawn from any one case, but it may be of some significance that in the following year when 47 such laminectomies were done and the use of gelatin sponges was restricted no postoperative drainage occurred. A minimal contamination which the body usually would control without a clinical infection may lead to prolonged inflammation in the presence of foreign bodies. This becomes a matter of increasing importance, since there is a general tendency among various infectious organisms to become resistant to antibiotics. Most staphylococci that cause hospital infections are resistant to penicillin, and the majority are also resistant to other antibiotics.

In the three cases of infected brain foci reported here, antibiotics prevented a

spread of the infection, so that blood and spinal fluid cultures remained sterile. Clinical improvement promptly occurred as soon as the bulky sponges were removed. In all likelihood wound contamination was not provided by the sponges, but a secondary infection became aggravated and prolonged by their presence. The interference of a foreign-body reaction with the defense mechanism against infection has recently been well illustrated by S. D. Elek * in experiments on human volunteers. He demonstrated that the potentiating effect which small sutures bring to infected wounds is in the order of 10,000-fold.

It is not concluded from these studies that absorbable sponges should be abandoned or that generous packing with them in a wound will necessarily cause low-grade infection, abscesses, or large scars. Their established property of promoting hemostatis has only been confirmed here. On the other hand, it becomes important to prevent, as far as possible, the complications that at times do occur with the sponges. This, it would seem, can be done in essentially three ways: First, by using as small amounts of the sponges as possible, none at all in potentially infected wounds, and by avoiding prolonged exposure of the porous sponges to contaminated air. Second, the sponges should be thoroughly compressed so that large air bubbles are eliminated and not brought into the wound. Third, in many instances, the hemostatic agents can be removed from the bleeding area before closure of the wound without renewal of bleeding again. Hemostatic sponges may be left in place while the wound is being prepared for closure, while bleeders are being cauterized or tied, and while the wound is irrigated. There will often be time enough for hemostasis to reach such a degree that the removal of the sponges, if gently done, will not cause further bleeding. The old surgical rule that foreign bodies of any kind should be avoided in wounds, if at all possible, still holds as true as ever.

* Elek, S. D.: Personal communication to the author.

Summary

A review of the literature on absorbable hemostatic sponges has revealed that there are wide discrepancies in the data regarding absorption time and tissue reaction.

A number of observations of wound infections following implantation of sponges have been accumulated both in experimental and in clinical surgery.

Further experimental studies regarding absorption and tissue response of hemostatic sponges are presented and include some unfavorable observations.

Two cases of brain abscess and one of an epileptogenic focus following implantation of gelatin are reported.

Methods are suggested to reduce the complications that at times occur in connection with the use of absorbable sponges.

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Experiences with the Polyethylene Tube in Esophageal Surgery

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Introduction

In the presentation of our study on the polyethylene tube in esophageal surgery, certain prefatory remarks are essential to establish the genesis of the polyethylene tube as a considered mode of therapy for cancer of the thoracic esophagus.

For the past decade and a half surgical extirpation followed by primary reestablishment of alimentary continuity has prevailed as the therapy of choice for carcinoma of the thoracic esophagus. During this period the progress of surgical techniques, advances of modern anesthesia, the practice of sound principles of thoracic surgery, the important adjuvants of blood replacement and antibiotics—all these have enhanced the applicability of this procedure. Nevertheless, it has remained an intervention of magnitude that has had to be offered to a group of patients who, because of age, associated diseases, and cachexia, were least able to react favorably to the severe operative stress that it imposed.

To date the facts indicate that in the most experienced hands results have been less than encouraging. Sweet * reported 12 five-year survivals in 390 patients, 11 having had lesions in the lower third of the esophagus. Resano † of Argentina, who for years has confined his surgical activity to diseases of the esophagus, reports 2 five-year cures in 1000 cases. Nakayama,[5] of Chiba, Japan, with a personal volume of 547 cases up to November, 1954, reports 10 five-year cures (in 78 resections), in 7 of which the lesions were in the lower esophagus. These figures are particularly significant because in Japan, with an inordinate prevalence of the disease, a public health program directed toward early detection has been in vogue for years. This program subjects every dyspeptic to x-ray screening, which includes a fluoroscopic study of the esophagus and an esophagram. Nakayama ‡ has related his high resectability rate (over 50%) to this program. In the United States DeBakey and co-workers [6] report a resectability rate of only 32% in 1377 collected cases. According to Ravitch and co-workers,[7] there have been no five-year cures at the Johns Hopkins Hospital. In the series of Parker and others,[8] there was 1 three-year survival in 170 patients with carcinoma of the esophagus.

Certainly operative mortality has not been conducive to enthusiasm for this drastic surgery. Sweet § had an operative mortality of 23.4% in carcinoma of the mid and upper esophagus, and 11.6% for the lower esophagus and cardia. Garlock's ‖ figures are almost identical. Nakayama's [5] figures are the lowest that are reported, i.e., 11.9% for lesions of the mid and upper esophagus and 5.3% for those of the lower esophagus and cardia. These findings must be considered exceptional. On the other

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* References 1, 2, and 3.

† Resaño,[4] cited by Ravitch.[7]

‡ Nakayama, K.: Personal communication to the authors.

§ References 1, 2, and 3.

‖ References 9 through 12.

hand, Parker and co-workers [8] had an operative mortality of 57.7% for the mid and upper esophageal lesions; Strieder,[13] 55.5% for the mid and upper esophageal lesions and 12% for those of the lower esophagus and cardia, and Cook County Hospital (all services), 80% for the mid and upper esophageal lesions and 68.7% for those of the lower esophagus and cardia. It is conceivable that in the average general hospital without special concentration on this program operative mortality more nearly parallels the latter figures and may in some instances be utterly prohibitive.

To counteract the pessimism created by these figures and in defense of the surgical therapy of this disease, Sweet ¶ has postulated from a careful analysis of his figures that the incidence of five-year survivals should be 34% for patients with lower esophageal lesions and 14% for those whose growth is higher up, with an over-all five-year survival for cases at all levels of 27%. These results, he states, are not unlike those considered satisfactory in the treatment of carcinoma of certain other regions of the body. Despite this optimism and justifiable postulation, the facts still stand. The results of the operative treatment of carcinoma of the thoracic esophagus have been disappointing, and the operative mortality has been discreditably high in most cases, and for several reasons, the chief of which are, first, the disease itself, and, second, the topographical anatomy of the thoracic esophagus.

1. The disease is insidious and remains asymptomatic long enough to thwart early recognition. Dysphagia, the cardinal symptom, does not herald the disease and may not appear for months after the establishment of the pathology. In short, there are no early symptoms to parallel early pathology. The disease also tends in most cases to early metastasis, an observation that may be associated with the absence of the serosal covering about the esophagus.

2. As to anatomy, the esophagus is situated in close relationship to other vital structures and, as demonstrated by Ravitch and co-workers,[7] the extensive lymphatic drainage to the nodes anterior to the aortic arch, in the hollow of the aortic arch, and to the mediastinal and parietal pleura precludes definitive cancer surgery of the en bloc, encompassing type, except at the lower end of the esophagus. The technical complexities parallel the anatomic height of the lesion. It is now generally affirmed that lesions of the lower end, whether epidermoid carcinoma or adenocarcinoma, have a higher resectability rate and give better results in long-term survivals.

It is our present contention, in the light of our surgical experience and that of others, that surgical resection with alimentary continuity should be performed only in favorable cases if the operative mortality and salvage rates are to be kept within a range that does not unjustly discredit the procedure. Selectively used, the procedure is, in our opinion, the best available form of therapy for palliation and cure in this disease. Since resectability rates are low (as previously mentioned, 32% in a collected series of 1377 cases and 16% in 119 cases at Harlem Hospital), some 70% to 80% of the victims of this scourge are left for treatment by some other method. It is important, therefore, that for this large body of patients we seek a method of effective palliation.

Gastrostomy or jejunostomy for alimentation is poor palliative therapy for a disease in which the most distressing symptom is inability to swallow—even one's own saliva. To meet this, esophagostomy [6] as a shunting procedure without resection has been tried. In our hands it has been so disappointing that we have completely abandoned it. Simple bouginage with or without radiation, insertion of a Souttar tube—these are all nonoperative methods that have been used; but, considering their limitations and uncertain results, we decided to investigate the efficacy of the polyethylene tube. It must be admitted that, at the very outset, we

¶ References 1, 2, and 3.

considered it a not altogether controllable surgical maneuver.

General Data

Statistics on Use of Polyethylene Intubation

	No. of Cases
Total number of cases in which polyethylene intubation was done	14
Resection of esophageal lesion, followed by intubation	9
Intubation without resection of esophageal lesion	5
Retrograde intubation through gastrotomy	2
Intubation through esophagotomy below the lesion	2
Intubation through constricted portion of the esophagus	1

A polyethylene tube (Fig. 1) was used as a prosthesis in 14 patients classified as unsuitable for operative resection and esophagogastrostomy or esophagojejunostomy.

In nine of these cases resection of the esophageal lesion was done, followed by use of the connecting polyethylene prosthesis.

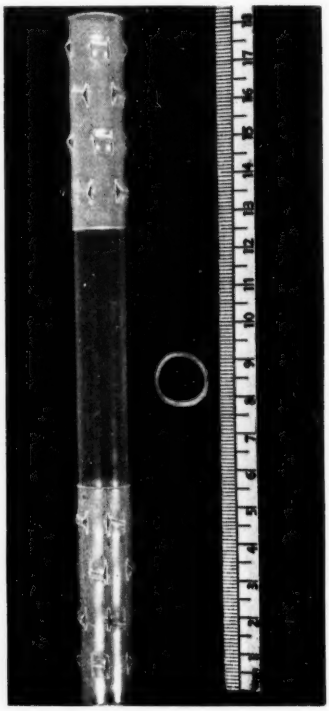


Fig. 1.—Polyethylene tube showing eyelets through which sutures are passed.

In the other five cases intubation was accomplished without resection of the esophageal lesion. In two of these intubation was effected in a retrograde fashion through a gastrotomy. In another two cases intubation was carried out through an esophagotomy performed below the lesion. In these four cases the lesion was dilated in retrograde fashion and the plastic tube was then anchored in position. In the one remaining case intubation was performed through the constricted portion of the esophagus by splitting and excising enough of the involved segment to make room for the tube. This was the equivalent of a bypass or shunt procedure.

In 10 cases the approach was through the right chest. In two lesions of the lower esophagus a left thoracotomy was performed. Two other carcinomas in the distal third of the esophagus were operated upon through an abdominal incision.

Technique

Preoperatively, the patients were prepared with whole blood transfusions, protein hydrolysates, and infusions of dextrose with or without isotonic sodium chloride solutions, as the case warranted, in an attempt to correct anemia, negative protein balance, and dehydration. When it was feasible, the patient was placed on a liquid diet fortified by a protein concentrate of high value.

Esophagoscopy was performed to obtain a biopsy specimen and to measure the distance of the upper limit of the lesion from the incisor teeth. Bronchoscopy was also done to clear the tracheobronchial tree of secretions and to note invasion, fixation, or extrinsic pressure. The recognition of fistulization with the tracheobronchial tree interdicted the use of the tube. On the afternoon prior to operation, a duodenal tube was inserted to the level of the lesion and constant suction was maintained.

Thoracotomy was carried out in the suspended prone position in five cases. In this position two advantages are presented: the provision of the best possible exposure to

the posterior mediastinum and the creation of the least disturbance in physiologic function. When the patient is placed in the lateral position and the chest opened, respirations are impaired and the likelihood of anoxemia is increased because the position limits the expansion of the dependent unopened side. When the patient is suspended in the face-down position, breathing is much easier and pulmonary function is not impaired. In this position, with the chest open, the mediastinum retains its normal locus with a minimum or absence of mediastinal shift; maximum vital capacity is maintained, and ample unimpeded ventilation reduces the risk of anoxemia. The posterior mediastinum is reached by the most direct approach and the exposure is excellent, inasmuch as the lung and heart fall away by their own weight and traction is thus avoided. Pooling of blood is away from the operative field and may be more readily controlled at its source.

In the prone position, for mid and upper lesions, the chest was entered through an incision in the fourth or fifth interspace, depending on the location of the lesion. Small one-half inch (1.27 cm.) segments of the adjacent ribs were removed posterior to the angles, and a rib spreader was introduced to give what was always an exceedingly adequate exposure. When the right anterior lateral position was used, the incision was also made through the fourth or fifth interspace, with section of the costal cartilages for needed exposure. For the lesions in the lower third, a left lateral approach was made through the sixth intercostal space with posterior section of the adjacent ribs.

In the right chest, after division of the azygos vein above and the pulmonary ligament below, the mediastinal pleura overlying the esophagus was incised and the esophagus exposed for dissection. In cases in which esophageal resection was done, it was obvious that malignant tissue, because of invasion and fixation, had to be left behind on the trachea, aorta, bronchus, vena cava, or in the lymphatic glands. In a case where resection was deemed injudicious, the site of the obstruction was incised and as much of the lesion removed as was necessary to provide a suitable bed for the polyethylene tube.

The method of intubation in the resected esophagus is as follows: The plastic tube is first inserted into the proximal end of the esophagus, making certain that at least 4 cm. of the esophagus overlaps the end of the tube. It is important to use a tube that fits snugly into the esophagus. A purse-string suture 1.5 cm. from the cut end, with each stitch going through the entire wall of the esophagus and tied just below the proximal cuff of the tube, is a simple but effective method of appositional union. This anastomotic suture must provide watertight and airtight closure. A few interrupted sutures, usually four, are then placed through the distal cuff and the esophagus for adjunctive fixation. For the caudal or distal anastomosis, the procedure is identical, with the anastomotic suture placed just proximal to the cut end of the esophagus. At the conclusion, with the tube lying in its bed, both esophageal ends should be free of tension; actually a certain slack is desirable. The anastomotic sites are enclosed with a flap of raised parietal pleura, but the mediastinum was not closed as suggested by Berman;[15] we chose, instead, to maintain confluence of the mediastinal and pleural spaces. This was done on the principle that a pleural collection, whether fluid or air, is more amenable to effective management than a mediastinal collection. We expected postoperative collections and got them to some degree in every case. In the one case in which a careful and complete mediastinal closure was done, an acute tension pneumomediastinum developed with explosive suddenness on the second postoperative day and would have caused an exitus had it not been for prompt surgical mediastinotomy and tracheostomy.

It must be clearly understood that the appositional union of the tube and the esophagus is a temporary contrivance that will function effectively only as long as its in-

tegrity exists; that it is subject to a dynamic interplay of mechanical stress factors that may at any time impair the integrity of the anastomosis, such, for example, as coughing, respiratory distress, the swallowing reflex, stomach distention, and the natural retractile tendency of the cut ends of the esophagus.

Later in the series, tantalum mesh (Fig. 2) was introduced to improve the technique of anastomosis. This was made with 00 Atraumatic silk passing from the tantalum mesh through the entire thickness of the esophagus, through the eyelet in the cuff of the polyethylene tube, and finally out through the entire thickness of the esophagus again, and through the piece of tantalum mesh wrapped about the outside of the esophagus. This suture is tied, and the same procedure is carried out on the opposite side of the tube. The ends of both sutures are then tied together, giving watertight closure.

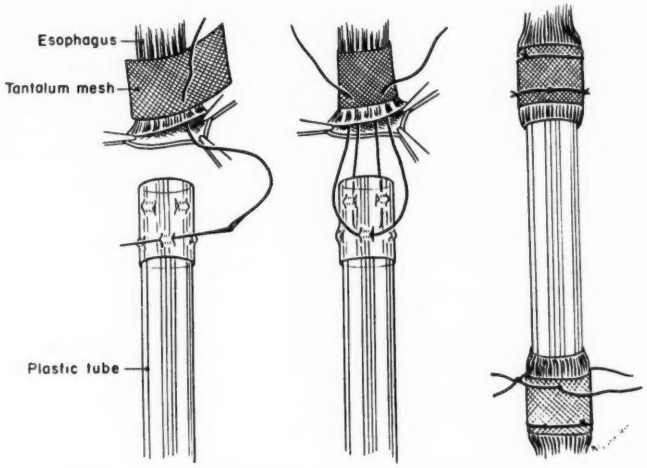


Fig. 2.—Technique of suturing plastic tube to esophagus.

It is often necessary to dilate the esophagus digitally before inserting the tube, and it may be necessary to bend the tube in order to insert it into the distal segment. A Levine tube is threaded through the polyethylene tube into the stomach. The chest cavity is then mechanically irrigated with saline, and the chest wall is closed. Thoracic drainage is instituted through two large catheters, one extending below the incision to the posterior axillary line and another to the mediastinal area. On occasion, anterior decompression for air was done through a catheter or needle at the second interspace in the midclavicular line. The catheter and Levine tubes are attached to a suction apparatus.

If a leak is demonstrated after the ingestion of methylene blue solution on the fifth day, a Stamm gastrostomy is performed for the purpose of alimentation and maintained until the anastomosis is sealed over. Removal of the chest catheter is dependent on the existence of leakage. At first patients were started on fluids on the fifth day, and then gradually given a more liberal soft diet, usually puréed foods, if leakage had not occurred. Otherwise they were fed by gastrostomy until the leakage stopped, usually in three to five weeks. The gastrostomy was then allowed to close spontaneously. We are now committed to fluids by the Levine tube up to the 10th day, with the use of a complementary gastrostomy for both alimentation and decompression when clinical developments suggest its desirability. Antibiotics administered postoperatively have undoubtedly contributed significantly to the control of infection.

In our most recent cases a different ap-

proach has been developed. In lesions of the lower third of the esophagus, the abdomen is first explored in order to decide whether the area is resectable. If it is decided that an esophagogastrostomy is not feasible, a gastrotomy is performed and the esophageal lesion is dilated in a retrograde fashion by bougies and digital pressure. A plastic tube is then inserted over the duodenal tube. The tube is anchored to the lower end of the esophagus or the cardiac portion of the stomach. Similarly, for nonresectable carcinomas in the mid-third of the esophagus, the esophagus is exposed through a right thoracotomy. An esophagotomy is performed well below the lesion. The constricted area is dilated in a similar fashion by bougies and digital pressure. The plastic tube is anchored in place by several interrupted 00 silk sutures. The esophagotomy is closed in two layers—00 chromic interrupted sutures for mucosa and 00 silk interrupted sutures for the submucosa and muscularis. The mediastinal pleura is approximated over the esophagotomy.

In our first two cases through this approach, the gastrotomy was converted into a Stamm gastrostomy for supplementary alimentation for the first week. However, we have found this to be unnecessary and subsequently intend to close the gastrotomy after the insertion of the plastic tube.

Postoperative Course and Complications

The cases will be divided into two groups: first, those in which the tube was inserted through a gastrotomy or esophagotomy without resection of the lesion, and, second, the group with resection and insertion of the tube.

The only complication in the group without resection of the lesion was a small wound separation at the upper angle of the abdominal incision. This patient had a low plasma protein and was in a poor state of nutrition.

In the second group, those with resection of the carcinoma, no case had an uneventful postoperative course. Most complications were a sequel to the procedure and resulted from leaks with gross contamination of the mediastinum and pleura, incidentally associated with the complications of pneumonitis and pulmonary atelectasis. A listing is as follows:

1. *Involvement of the Pleural Sac with Collections of Air or Fluid.*—Practically all cases had a pleuritis. There was a significant empyema in three cases, effectively controlled by closed drainage. Pleural effusion and pneumothorax were present to some degree in all cases during the postoperative course. Tension pneumothorax was present in two cases.

2. *Involvement of the Mediastinum.*—There was no evidence of clinical mediastinitis in any case, notwithstanding known contamination during operation and by leaks after operation. Pneumomediastinum was recognized in two cases and a serious tension pneumomediastinum in one case.

3. *Subcutaneous Emphysema.* — There was one acute and extensive manifestation of subcutaneous emphysema associated with the tension pneumomediastinum. In three other cases subcutaneous emphysema was noted, but was insignificant as well as innocuous.

4. *Edema of the Glottis.*—Edema of the glottis developed in two cases requiring tracheostomy.

5. *Marked Distention of the Vagotomized Stomach.*—This occurred in five cases and was managed more effectively by gastrostomy than by Levine tube suction.

6. *Atelectasis or Pneumonitis.*—A contributing factor to death in four cases.

7. *Pulmonary Embolus.*—Fatal in one case.

8. *Coronary Occlusion.*—Fatal in one case.

9. *Chest Wall Sinuses.*—Chest wall sinuses, incidental to leaks, eventually closed in the favorable results.

These represent the significant complications encountered.

Report of Cases

CASE 1.—A 64-year-old patient was admitted,

complaining of progressive dysphagia and weight loss of eight months' duration. Dysphagia became very severe three months prior to admission, associated with constant regurgitation.

Physical Examination.—Blood pressure 100/78, pulse rate 60, respirations 18, temperature 98.2 F. General appearance was that of a poorly developed, emaciated Negro man with marked weakness, presenting a deformity of the cervical spine. Chest x-ray showed marked pulmonary emphysema, and there was very little pulmonary exchange. His general condition was extremely poor.

Laboratory Studies.—Red blood cells 3,580,000; blood chemistry normal; hematocrit reading 25.2; albumin 2.8 and globulin 3.2 gm. per 100 cc.; A/G ratio with reversal at 0.74.

Esophagram revealed a complete obstruction at the level of the aortic bulb. The patient was prepared for surgery, receiving both blood and protein hydrolysate (Amigen). Meperidine (Demerol), 50 mg., depressed his respiration on the day of operation, so that operation was cancelled and rescheduled.

Operation.—On Feb. 17, 1953, a subtotal esophagectomy through the right chest was performed, and a polyethylene tube was inserted to restore continuity. The operation was uneventful, and the patient received appropriate underwater suction drainage.

Postoperative Course.—Postoperatively, the patient developed abdominal distention on the third day, and a Stamm gastrostomy was performed for decompression primarily and also for alimentation. On the 8th postoperative day pleural effusion was present, and on the 14th day an esophageal fistula had manifested itself.

The patient received continuous underwater drainage, antibiotics, and fluid with electrolyte supportive therapy. One month postoperatively, no evidence of esophageal fistula could be demonstrated by methylene blue swallow, and liquids were well tolerated thereafter. The empyema following the esophageal fistula drained less and less and finally ceased. Thereafter the patient was permitted a soft diet, and the gastrostomy tube feedings were discontinued. The patient was out of bed and spent the greater part of the day eating. His appetite was phenomenal. He gradually gained weight.

The patient maintained fair nutritional balance, and on June 29 he was found lifeless in bed.

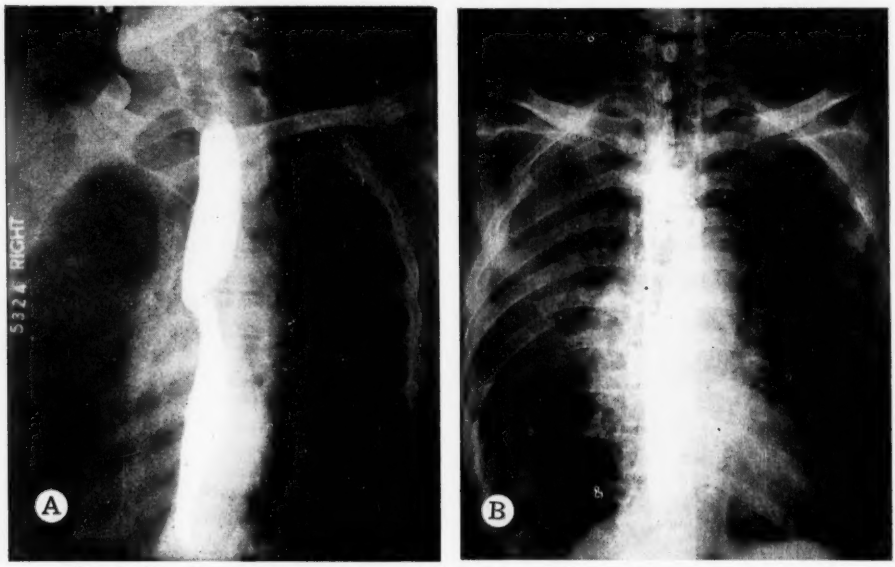


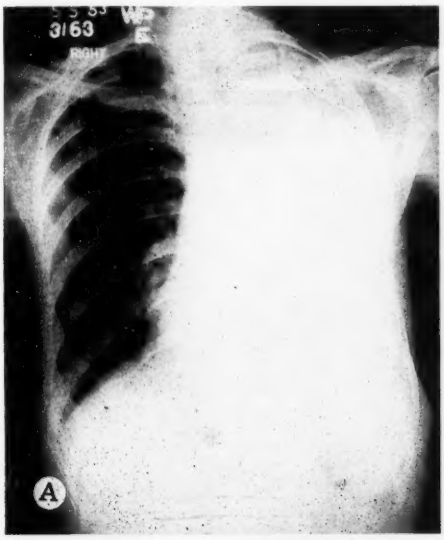
Fig. 3 (Case 1).—Carcinoma of the mid third of the esophagus with resection and insertion of polyethylene tube. Esophageal fistula is demonstrated at proximal end of tube.

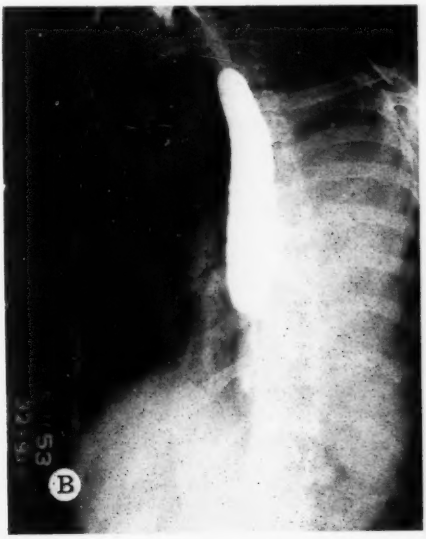
Comment.—Following resection of the esophagus and replacement with a plastic tube, this patient developed such complications as marked abdominal distention, empyema, and esophageal fistula (Fig. 3).

Case 2.—A 65-year-old woman was admitted with a one-year history of dysphagia, loss of weight, and epigastric distress. On admission to Harlem Hospital on the Medical Service, she was found to have a massive left pleural effusion. Work-up revealed a carcinoma of the lower third of the esophagus. The patient was emaciated and had poor pulmonary reserve and mild cardial damage.

Operation.—Operation was performed through the left chest in the lateral position. An amount of 1500 cc. of serosanguineous fluid was found in the pleural cavity. The lung was so frozen to the esophagus that the lesion could not be palpated or approached. A small opening was made in the supradiaphragmatic portion of the esophagus, and the esophageal lesion was dilated digitally in a retrograde fashion. The duodenal tube was pulled down and a polyethylene tube was threaded on the duodenal tube, and in that way the latter was inserted into the upper portion of the esophagus. The polyethylene tube was then fixed to the lower end of the esophagus and the esophagus was closed.

Postoperative Course.—The postoperative course was uneventful, with no fistula formation. One month after operation it was decided to give a course of deep x-ray therapy. The patient apparently sloughed out some of the esophageal lesion and developed an empyema, which was treated by intercostal drainage. Drainage cleared within two weeks, and the patient was discharged. She was able to eat after the operation, and during the first four months she gained 15 lb. (6.8 kg.) in weight.





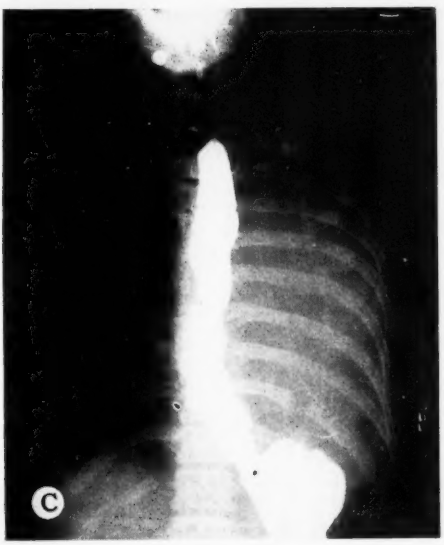


Fig. 4 (Case 2).—Carcinoma of the lower third of the esophagus with pleural effusion. Polyethylene tube was inserted through esophagotomy without complication.

The patient was found dead in bed 11 months following the operation.

Comment.—This patient lived 11 months without any of the explosive complications secondary to resection of the lesion and intubation (Fig. 4).

Case 3.—A 67-year-old man entered the hospital with a two-month history of difficulty in swallowing solid and liquid food. There had been a weight loss of 25 lb. (11.3 kg.) during this period of time.

Physical Examination.—Physical examination revealed an elderly, emaciated dehydrated man. Esophagram and esophagoscopy demonstrated a lesion 36 cm. from the incisor teeth. Biopsy was reported as showing malignant squamous epithelial cells.

Operation.—The patient was prepared for surgery with blood transfusions and protein hydrolysate. An exploratory laparotomy was performed, at which time the lesion was found to be inoperable —fixed to the diaphragm and aorta and with nodes along the celiac and aortic chain. A gastrotomy was performed in the fundus, and the lesion was dilated manually until a plastic tube could be inserted in a retrograde fashion. The tube was anchored to the cardiac end of the stomach with interrupted 00 silk sutures. The gastrotomy was closed, and a Stamm gastrostomy effected through a stab wound.

Postoperative Course.—Postoperatively, the patient had an uneventful convalescence. He was fed on the second day through the gastrotomy. Following the ingestion of iodized oil (Lipiodol) to determine the patency of the plastic tube, the gastrostomy was allowed to close on the 10th day. The patient gained 20 lb. (9 kg.) since the time of operation, and he was discharged on the 21st day. He is now at home, three months since the operation, and is going about his daily routine. His diet consists of well-chewed soft food. There apparently has been no difficulty in eating and swallowing.

Comment.—A plastic tube was inserted through a gastrotomy opening in a retrograde fashion, after it had been ascertained that the lesion was inoperable. The patient has had a completely uneventful postoperative course and has gained 20 lb. (9 kg.). We now feel that the gastrotomy is no longer necessary when this procedure is carried out in this fashon (Fig. 5).

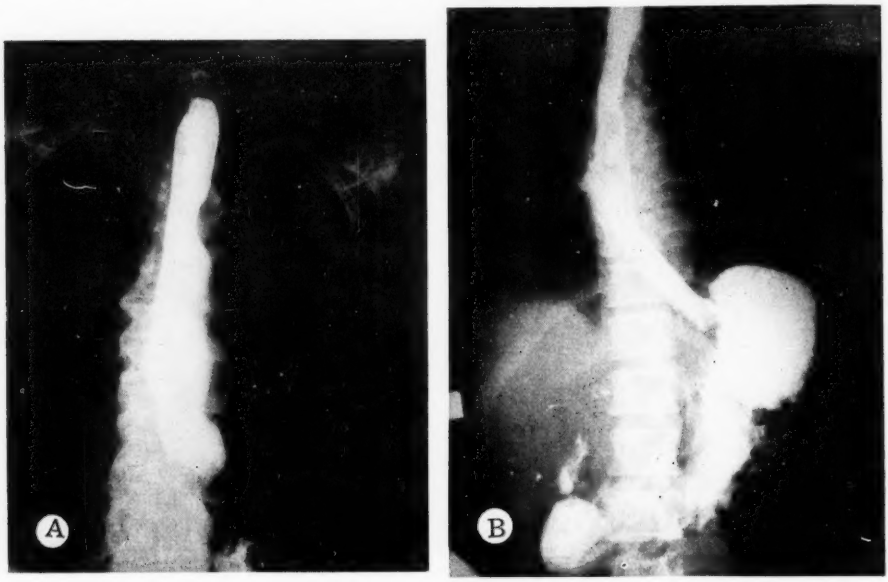


Fig. 5 (Case 3).—Carcinoma of the lower third of the esophagus with polyethylene tube inserted through a gastrotomy. Patient is living 3 months following procedure without any complications.

Results

1. There were three deaths in the immediate postoperative period: one on the 3rd day, of coronary occlusion; one on the 11th day, of pulmonary embolus, and one on the 2nd day, of heart failure.

2. There were five other deaths within a three-month period. Four have been classed as operative deaths, because the postoperative complications of low-grade empyema, pneumonitis, and atelectasis apparently contributed in great measure to the exitus. One patient, intubated through a gastrotomy, did not have any complications contributing to his death but died of the disease itself.

It must be recognized that these patients were in an advanced stage of local carcinomatous spread with a serious intrusion on vital structures.

Operative mortality for the series therefore is 42.8%, a not insignificant figure.

3. There were six patients who survived the postoperative period to live for 3 to 11 months. Complications incident to leaks were all successfully managed and did not significantly disturb the progress of recovery and convalescence.

4. Deglutition was restored in the favorable results, but it was necessary for patients to masticate food thoroughly and to render it semifluid for satisfactory ingestion. It was our impression that, at best, deglutition with the tube was about 60% to 70% of normal. Nutrition definitely improved, as evidenced by weight increase.

5. There was no dislodgment of the tube from its bed in any case. It seemed that this potential danger lessened with time.

General Comment

The polyethylene tube was first used by Berman,# of the Sinai Hospital, in Baltimore. Polyethylene was chosen because it has negative water absorption; that is, it is nonwettable, nonporous, easily sterilized, semiflexible, and nonabsorbable in human tissues, and it is not altered by foods, alkalies, or acids. Beck and co-workers [17] showed that polyethylene tends to be surrounded by a nonadherent fibrous capsule when placed in living tissue. Spealman and co-workers [18] proved that polyethylene possesses no toxic reaction. Relative to its application as a bridge for the resected esophagus, Berman demonstrated that a hemorrhagic, serofibrinous exudate forms about the tube and is converted first into granulation tissue and ultimately into dense fibrous tissue. It has been observed that in the experimental animal squamous-cell epithelium grows out from the esophagus at either end and tends to line the new fibrous tube. It was also noted experimentally that within 10 or 12 days the silk sutures, which anchored the tube to the esophagus, sloughed through the thickness of the esophagus and were healed over with fibrous tissue. Our clinical experiences are at variance with this pattern in the experimental animal. It has actually been our observation that from the time of the insertion of the tube into the esophageal ends, appositional union of the tube and the esophagus is a vulnerable contrivance, subject to impairment at any time as a result of an interplay of dynamic stress factors such as may arise from coughing, the swallowing reflex, the natural retractile tendency of the esophageal ends, distention of the stomach, etc. It is also possible that the circular anastomotic suture applied to a diseased, edematous, or inflamed esophageal wall may cut through at any time after operation and before the formation of a satisfactory adventitious capsule. All this, of course, creates a potential for leaks and may complicate or disturb fibrogenesis around the tube. These considerations suggest that, on the part of the surgeon, there must be an awareness of and a vigilance for the immediate recognition of complications arising from leaks that may occur at any time from the first postoperative day on—complications that develop outside the fibrogranulation compartment, to wit, mediastinitis, empyema, pneumothorax, pneumomediastinum, etc. These morbid entities, from our experience, do occur, but may be successfully managed and certainly need not be fatal.

As far as the polyethylene tube is concerned, we have experimented with various modifications of the tube and methods of suturing. It has been deemed important to have a cuff of at least 4 cm. overlapping the tube, inasmuch as the esophagus tends to retract longitudinally. Most important is that, with the tube lying in its bed after completion of the anastomoses, there should be no tension at either end and a sufficient slack should be present to provide for the longitudinal retractile tendency of the esophageal ends. A circular suture, no matter how it is placed, through the esophagus or just merely tied around the esophagus and tube under the cuff, is more secure than interrupted silk sutures and, in our opinion, is essential for appositional union. Any

References 14, 15, and 16.

other sutures that are introduced should be purely for additional fixation of the tube. Since the silk sutures are supposed to slough through the wall of the esophagus by the 10th or 12th day, we have attempted to control this by wrapping a piece of tantalum mesh around the outside of the esophagus at the anastomotic sites. In this fashion the silk sutures are maintained by the tantalum mesh on the outside of the esophagus and by the polyethylene tube on the inside. The patients invariably develop leakage from the upper end of the tube, which we find usually ceases in three to five weeks with successful management.

Postmortem examinations are quite illuminating. In patients who lived with the polyethylene tube for over six months, there was revealed a fibrous sheath uniting the esophageal ends and measuring from 0.8 to 1 cm. in thickness and tightly wrapped around the tube. Sections failed to reveal epithelization at this stage from either end of the esophagus. A recent postmortem examination following death on the 11th day of pulmonary embolus showed a thick fibrogelatinous sheath about the esophagus, with the sutures held in place by the tantalum mesh. There was evidence of leakage at the upper anastomotic site.

The question of drainage is important. The pleural cavity must be drained for air and also for fluid, for collections incident to surgery or collections incident to the development of fistulae or leaks. It is important to watch the opposite chest for a possible pneumothorax. There were two in our series. In extensive lesions involving the trachea or bronchus, the leakage of air may come from these structures as well as from the lung. In one case an empyema developed after the patient started to eat without permission. This complication was adequately managed by catheter drainage, aspiration and the liberal use of antibiotics, and the institution of a temporary Stamm gastrostomy for alimentation.

It should be noted that in four of the five cases in which the esophagus was intubated without resection the results were satisfactory and practically without complications. One such patient lived 11 months, another lived 6 months, one lived 5 weeks, and one is now leading a normal life 3 months after operation. All these patients experienced no difficulty in swallowing a soft well-masticated diet and experienced none of the complications exemplified by the other group.

Concerning the question of postoperative radiation, it has been demonstrated that irradiation has no untoward effect on polyethylene.[19] Actually, the properties of the irradiated tube show an improvement in form stability at elevated temperatures, in resistance to solvents, and in tensile strength. Only one patient was irradiated postoperatively, and she developed an empyema secondary to sloughing out of carcinomatous tissue.

Summary and Conclusions

A summary is presented of our experiences with 14 cases of carcinoma of the esophagus in which a polyethylene tube was used as a palliative prosthesis.

In four of the five cases in which the plastic tube was inserted without resection of the lesion, the results were satisfactory and the complications minimal.

In eight of the nine cases in which the esophagus was resected and the plastic tube used to bridge the gap, major complications resulted from the inherent vulnerability of the anastomosis of the tube and the esophagus. Leaks are the basis of the complications, and the management of these complications is discussed.

In two cases, the patients died in the immediate postoperative period of coronary occlusion and congestive heart failure, secondary to myocardial damage.

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Palliative Forequarter Amputation for Recurrent Breast Carcinoma

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Interscapulothoracic, or forequarter, amputation is a disfiguring operation and is done much less frequently than its counterpart in the lower extremity. It is performed most frequently for malignancy, although selected benign tumors, osteomyelitis of the shoulder girdle, extensive injuries, and aneurysms have been treated by this type of surgery.

In malignancy, forequarter amputation is usually done as a curative measure for primary bone malignancy, malignant melanomas,[1] fibrosarcomas,[2] and similar tumors which either cannot be removed mechanically by another method or which would have a much poorer curative rate with less extensive procedures.[1] Few extremities have been amputated as a palliative procedure for carcinoma of the breast. Pack in 1942[3] cited Buchanan's report of one hundred forty-one collected cases of forequarter amputation prior to 1900, four of them being for recurrent carcinoma of the breast. He summarized the cases from 1900 to 1942 and found 180, again 4 being for recurrent breast carcinoma. To these cases he added another 31, none being for palliation for this malady. Pack concluded, in a discussion of radical amputations for cancer, in 1947,[4] that occasionally they had a definite place in palliative therapy.

Biasini[5] states that carcinoma of the breast can sometimes be an indication for forequarter amputation. Smyth[6] in 1946 included such cases among his indications but stated that the need for such surgery had been lessened by radiotherapy.

Prudente[7] in 1949 reported six cases of recurrent carcinoma of the breast subjected to radical upper extremity amputation for pain. At the same time he put forth the thesis that a radical mastectomy should be combined with a forequarter amputation as primary therapy for certain selected cases, those with fixed axilliary adenopathy and/or mobile supraclavicular adenopathy in which no evidence of further spread existed. Haggart[8] performed this operation for palliation because of marked discomfort in a patient with a very malignant sarcoma of the shoulder girdle, and Wishner,[9] for a metastatic hypernephroma in a humerus.

Berman * in 1945 stated his opinion that pain alone should not be an indication for interscapulothoracic amputation, because this complication could be treated by rhizotomy or chordotomy. He added that any surgery for pain should be done relatively early, because of the tendency of long-standing pain to persist postoperatively. He did feel, however, that ulcerated and infected axillary lesions justified radical surgery.

The use of forequarter amputation for palliation was not mentioned in discussion of the procedure by Berthola,[12] Grimes and Bell,[13] Pontes,[14] Slocum,[15] and Strode and Fennel.

Two cases of interscapulothoracic amputation of painful flail extremities due to infiltration of the brachial plexus and the subclavian vessels by recurrent breast carcinoma are reported.

Report of Cases

CASE 1.—A woman first noted dimpling in the skin of her left breast in December, 1948. Ulcera-

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From the Department of Orthopedic Surgery, Carle Memorial Hospital and Carle Hospital Clinic.

* References 10 and 11.

tion developed May 12, 1951. She was first seen at the Carle Hospital Clinic for this on May 14, 1951, at which time there was a 3 cm. mass in the breast with ulceration and palpable axillary glands. A radical mastectomy was done two days later, followed by irradiation. Minimal edema appeared in the ipsilateral upper extremity nine months later. This gradually increased, and pain referred to the hand began 18 months postoperatively. This increased in severity and was not helped by stellate blocks, tetraethylammonium (Etamon), or cortisone. Twenty-seven months postoperatively the arm was useless, flail, and painful. Axillary ulceration developed 34 months after mastectomy. On April 13, 1954, almost two years after surgery, a forequarter amputation was performed, followed again by x-ray therapy. The postoperative course was uneventful, and the patient gained weight, did all of her housework, and drove her own car. Her only complaint was that of mild phantom discomfort. In February, 1955, skin metastases began to develop. They were controlled by irradiation. She developed back pain in the summer of 1955. X-rays in August showed almost complete destruction of the body of the ninth thoracic vertebra and loculated pleural effusion in the left chest. She has improved on bed rest at the current time.

Note.—Since this article was submitted for publication the patient died in February, 1956.

CASE 2.—A woman had a mastectomy in January, 1954, for a lesion noted for two months. Ten months later pain and swelling of the entire upper extremity began. She was first seen in the Carle Hospital Clinic on Jan. 3, 1955, with moderate edema of the extremity and masses in the axillary and infraclavicular areas. The chest x-ray was negative, and a forequarter amputation was done on Jan. 20, 1955. Her postoperative course was uneventful except that she had moderate phantom discomfort. She began to do a little housework. A cough began two months after the amputation. Almost four months postoperatively she developed abdominal distention and jaundice, deteriorated rapidly, and died, on May 20, 1955.

Both of these procedures were definitely done with only palliation as a goal, despite no evidence of distant metastases. Both patients had had very painful and useless extremities. To be free of this pain, both accepted amputation with no promise of cure of their disease. The first patient had had a very worth-while result, not developing any clinical metastases for 10 months or any symptomatic metastases for 14 months after the amputation. Although she has phantom discomfort, it is mild and not bothersome.

The result in the second patient is open to question. Her four months of life following the amputation were definitely more comfortable, despite phantom sensations of moderate degree, and her final illness was relatively easy and very rapid. It was the opinion of the internist and the surgeon who cared for her that the procedure was worth while.

During this same period a third case was seen with a similar situation. It was elected to treat this patient conservatively, because pain and dysfunction had not yet become severe enough to warrant amputation.

Technically, the Berger type of amputation was performed, as outlined by Slocum.[16] The scapula and the clavicle lateral to the sternomastoid insertion were removed along with the upper extremity. Two points should be noted. The first is that the skin of both patients had been irradiated after the original mastectomies. Skin flaps had to be more generous than usual because of the decrease in elasticity, secondary to the irradiation. The second is that postmastectomy scarring around the subclavian vessels may necessitate more careful dissection than usual and that the recurrent carcinoma may have infiltrated these vessels and the brachial plexus to such a degree that they may be difficult or even impossible to recognize.

Although interscapulothoracic amputation for recurrent carcinoma of the breast will not be indicated often, it is a procedure which can be of great help to a patient with a painful functionless extremity in the absence of distant metastases.

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Prognosis and Early Diagnosis of Nonunion of Femoral Neck Fractures by Laminography

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Two decades of using metallic fixation in fractures of the femoral neck have produced thousands of cases, and the reported results show 80% to 90% union. However, certain of these fractures did not lend themselves easily to reduction or nailing and required secondary surgery to achieve this incidence of healing.

Often this situation manifests itself early in the postoperative period by a complete dissociation of the fragments, which is easy to recognize clinically and confirm by roentgenograms which show that the reduction or nailing is inadequate. When this occurs, secondary surgical procedures often are successful in achieving union with little or no increase in the period of disability. Unfortunately, this is not always the case, and incipient nonunion is often not evident until many months after the injury.

If the nail has remained in place and the fragments have not changed position after surgery, clinical examination is rarely helpful in diagnosing nonunion. Conventional anteroposterior and lateral roentgenograms show the position of the nail in the head and neck, bending of the nail, varus or valgus deformity, or some rotation of the femoral head. These findings may suggest impending nonunion, but postoperative films can rarely be taken with the limb in sufficient internal rotation to show the entire length of the femoral neck, and even if this were achieved the plane of the fracture is usually not well visualized. These factors mitigate against accurate early diagnosis or prognosis of nonunion. Indeed, it is not uncommon for a trial of weight bearing to establish the presence of nonunion nine months or a year after the original injury. Even after this length of time nonunion can be treated, but the earlier the diagnosis is made the more likely is treatment to be successful. The elderly patient who has been allowed to wait these many months for a diagnosis of nonunion stands a poorer chance of osteosynthesis and of functional rehabilitation than if failure had been recognized early in the postoperative period.

Of 39 patients requiring secondary surgery for fractures of the femoral neck, only 15, or 38.5%, were reoperated upon within eight weeks of their original surgery. The remaining 24, or 61.5%, had their secondary surgery deferred from 2 to 17 months after their original surgical reduction. Certainly the latter group is not a true indication of the length of time necessary to make a diagnosis of nonunion, but the first group of patients clearly indicates our incidence of early treatment of inadequate reduction and nailing. Early secondary intervention was always forced by a complete breakdown of the original nailing.

In order to aid in the early recognition of inadequately reduced or poorly apposed fractures of the femoral neck, we have employed laminograms. The laminogram provides information at regular intervals throughout the fracture site, regardless of

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the bulk of the buttock and pelvis, the position of the limb, or the plane of the fracture. The laminograms have been taken in the anteroposterior plane with the limb held in as nearly neutral position as possible. At 1 cm. intervals only three or four films are significant. With motored apparatus and fluoroscopic control, films may be taken at ½ cm. intervals and usually four or five films are necessary (Fig. 13).

Laminograms cannot be interpreted with regard to bone healing because in the femoral neck healing is largely endosteal and no periosteal callus is produced. There may also appear to be trabeculation across the fracture site in some distorted films. The only interpretation which we have placed on the laminograms in our series is the degree of apposition of the fragments. We believe that if the nail has been well placed apposition is the prime requisite for healing. We have estimated from the laminograms the percentage of apposition of the fragments at the fracture site. If four laminogram films are judged to be significant, the maximum amount of apposition ascribable to a single film is 25%. If apposition is present through only about half of a single film, this film would then be considered to show 12½% apposition. The sum total of apposition on the significant films of a set is a numerical means of expressing an estimate of the degree of apposition of the fragments.

In order to rule out the possibility of false interpretations, cadaver specimens

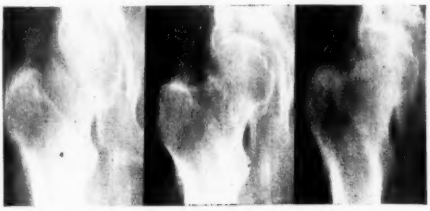

Fig. 1 (Case 1).—Laminograms indicate complete apposition through fracture site, center and right; at left, however, there is a defect in the superior portion. Complete apposition is rare, even in impacted fractures.

Fig. 2 (Case 2).—Anteroposterior and lateral roentgenograms show good impaction posteriorly but some defect anteriorly.

Fig. 3 (Case 2).—Laminograms show evidence of the defect as in Figure 2, but there is sufficient apposition to allow good healing in middle and posterior portions. Anterior defect persisted even after one year of uneventful weight bearing.

Fig. 4 (Case 3).—Lateral and anteroposterior views three months after nailing of a valgus fracture. No idea of the degree of healing can be obtained from these films.

were fractured and nailed in different positions and were vigorously impacted. Routine films and laminograms were taken in varying degrees of rotation, and every specimen, no matter in which plane it was rotated, always showed the same degree of apposition on the laminograms, but rotation often masked the true situation on conventional films.

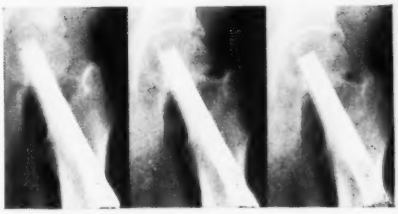

Fig. 5 (Case 3).—Laminograms of same case as Figure 4 show complete apposition at all points in each view. With this degree of apposition fracture was healed in 12 to 16 weeks. The patient has been weight bearing without symptoms for one year.

Among our cases it was uncommon to find 100% apposition, even in impacted fractures (Fig. 1). Most of the cases, including those which appeared excellent on conventional films, showed only about 60% to 70% apposition. Apparently this occurs because there is often some impaction at the time of fractures in which alignment of the fragdo not remain apposed (Figs. 2, 3). All of these healed, and, indeed, some fractures have healed with only 50% apposition. In

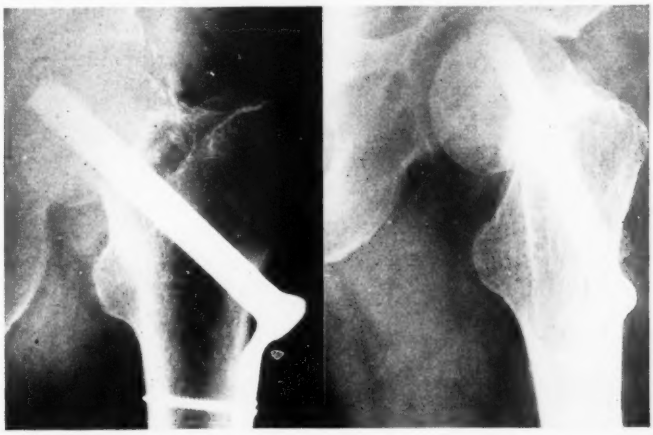

Fig. 6.—Anteroposterior and lateral roentgenograms show varus deformity rotation of the head.

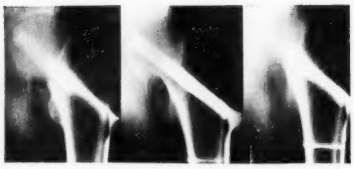

Fig. 7.—Laminograms show the head of the femur in good focus but fail to show the trochanteric region confirming the lack of apposition of the fragments. This patient had a nonunion.

this latter group of fractures the valgus deformities were often seen to heal despite the diminished amount of apposition of fragments (Figs. 4 and 5). A hip nailed in a position of varus rarely remains fixed by the nail long enough to heal or even be classified as a nonunion (Figs. 6 and 7).

Most significant in our study is a group of the fracture even though the fragments ments appears perfect and the nailing is perfect, but the laminograms show distraction of the fragments, which is not fully appreciated on conventional films. These cases have progressed to nonunion (Figs. 8-15).

Laminograms suggest that distraction of fragments which we attribute to absorption of bone may have been present from the time of the nailing.

It has been our custom to use nails with plate fixation in fractures of the femoral neck. These cases in which there has been diastasis at the fracture site might ultimately have become impacted if the nail had not been fixed with a plate and had been allowed to back out, but this can occur only with a sacrifice in the quality of fixation, and we believe that it is better to have a firmly fixed nail than one which loosens in the nail tract and thereby jeopardizes fixation. It may be that the Badgley nail may be part of the answer.

Although laminograms have mostly been invoked to establish the presence of nonunion, they may also be used to establish the presence of union. We have seen a case

Fig. 8 (Case 5).—Anteroposterior and lateral roentgenograms show a well-nailed and well-aligned fracture three months after surgery.

Fig. 9 (Case 5).—Laminograms taken at three months after surgery show almost complete lack of apposition of the fragments in each view confirming the suspicion of nonunion. At that time without changing the fixation, cortical and cancellous grafts were placed across the fracture site.

nailed with the proximal fragment rotated markedly in relation to the neck. After six months, though the fragments had not changed position, the surgeon believed there was little likelihood of healing. Laminograms showed sufficient apposition of the fragments to suggest that there might be union and a thorough trial of weight bearing has been in progress for more than a year without pain or change in fragments.

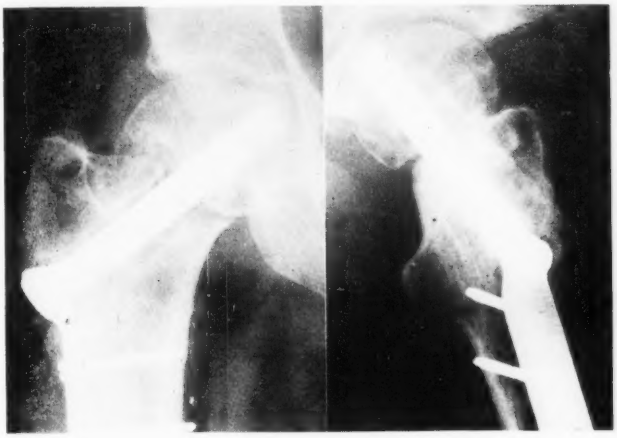

Fig. 10 (Case 5).—Anteroposterior and lateral roentgenograms six months after bone grafting.

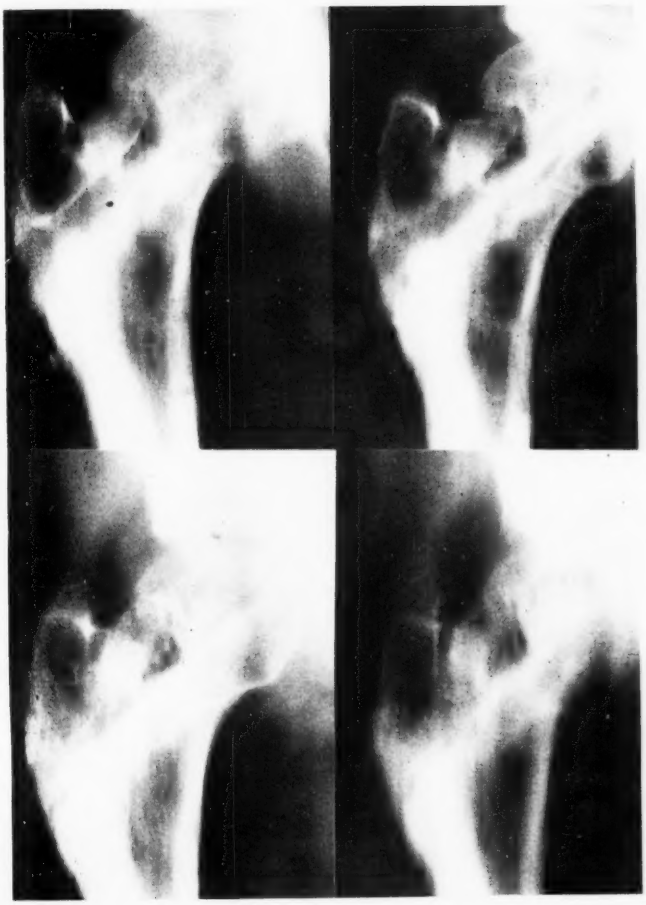

Fig. 11 (Case 5).—Laminograms 12 months after Figure 10 during which time the nail has been removed. The patient has since been weight bearing for one year and there are still defects in the fracture site, but three years after fracture there is no aseptic necrosis.

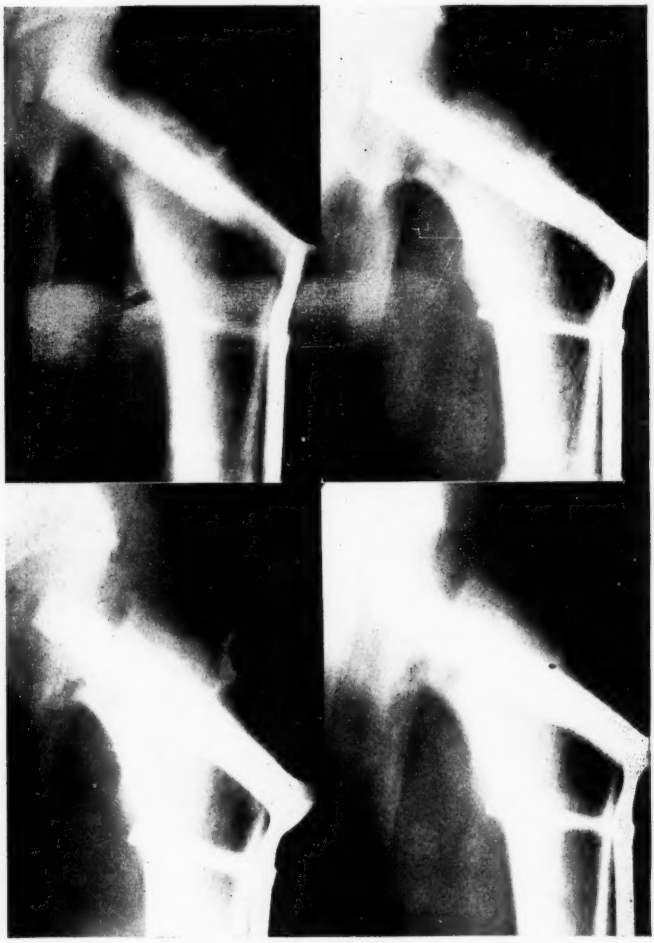

Fig. 12 (Case 6).—Postoperative laminograms show bending of nail and defects inferiorly and superiorly in all views. Degree of apposition of fragments is minimal and the prognosis was poor.

Summary and Conclusions

Laminograms are a means of estimating the degree of apposition at the fracture site.

A number of cases studied in this manner suggest that the degree of apposition of fragments in femoral neck fractures is significant in determining early which cases will heal and which will develop nonunion.

These studies have lead to our earlier intervention in cases with poor apposition of the fracture fragments.

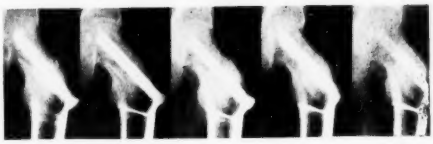

Fig. 13.—Laminograms after replacement of nail and addition of cortical and cancellous grafts. These films were taken at ½-cm. intervals, in contrast with other films in the series which were all taken at 1-cm. intervals.

Fig. 14 (Case 7).—Anteroposterior and lateral roentgenograms show a well-placed nail with the head of the femur slightly rotated into valgus position.

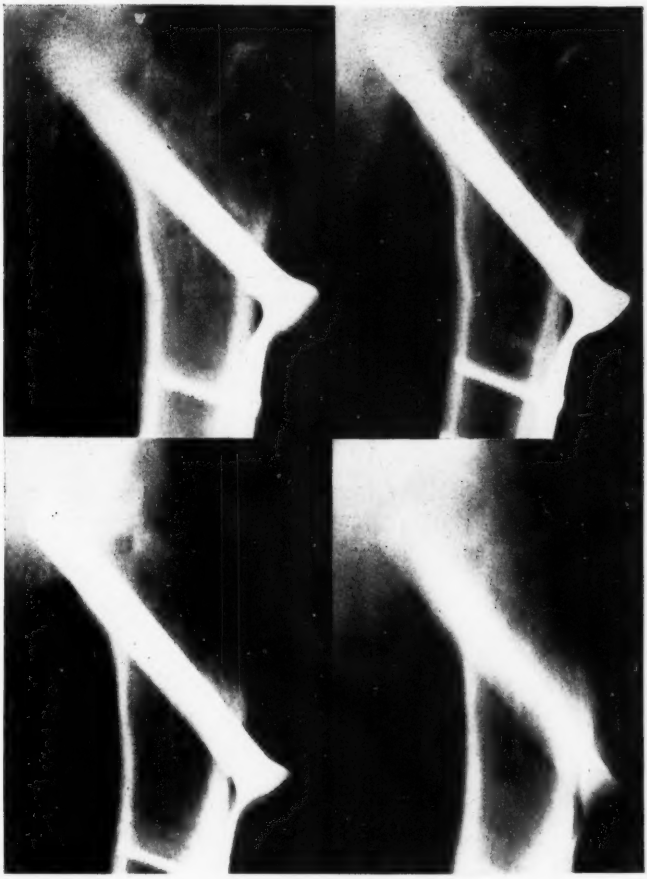

Fig. 15.—Laminograms show marked lack of apposition at the fracture site in all views and forebode subsequent nonunion.

Shock Occurring During Cardiac Surgery

Its Treatment with Levarterenol Bitartrate

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Since levarterenol (Levophed *) was first introduced into the practice of medicine, about 1950, many investigators have reported favorably on its unique faculty of elevating an apparently absent blood pressure to a readable and satisfactory level.† Many of these are laboratory or individual case reports. Some are series of assorted cases in which the drug was used to great advantage, and a few deal with its efficacy in myocardial infarction.‡ Four reports § mention the use of levarterenol in cardiac surgery and all are favorable.

However, there has not been published a series of cardiac and great vessel surgical cases in which the drug was used, particularly in which the resultant blood pressure changes were recorded. Our experience in 224 consecutive cardiac surgical cases with the same surgical team in the same hospital ‖ from 1951 to 1954 form the basis of this report. In 96 of these cases levarterenol was used, and in all but one it raised the blood pressure. The effect of this drug in these cases will be given in detail so that the data will be available for analysis by others interested in cardiac and great vessel surgery.

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* Levophed (brand of levarterenol) biartrate (also known as norepinephrine, *l*-arterenol, and Noradrenaline), supplied by Department of Medical Research, Winthrop-Stearns, Inc., New York.

† References 1 through 8 and 11 through 13.

‡ References 11 through 13.

§ References 2 through 6.

‖ From the Bailey Thoracic Clinic and the Service of Dr. Charles P. Bailey at the Doctors Hospital of Philadelphia.

All the patients were carefully prepared for surgery with medical management, and no patient was operated on while any further improvement in the function of the heart, lungs, kidneys, or general status could reasonably be expected. The decision as to when to operate was made by the entire team, i.e., the surgeon, cardiologist, anesthesiologist, and resident in charge. Despite the careful preparation, many patients were still in cardiac failure when brought to the operating room. Almost all were "poor" surgical risks and belonged to "Class 3" of the classification of the American Society of Anesthesiologists.

Premedication for all intracardiac operations was very light. All these patients received atropine or scopolamine 0.15 to 0.6 mg., hypodermically 15 to 45 minutes before induction of anesthesia. Over half received pentobarbital (Nembutal) or secobarbital (Seconal) 50 mg. orally, about two hours before surgery. This practice was discontinued in 1953, and from then on no barbiturate was given after bedtime of the day preceding surgery. In the better-risk extracardiac cases, morphine up to 10 mg. and scopolamine up to 0.4 mg. were given hypodermically 60 to 90 minutes preoperatively.

The anesthetic management of all the cases was similar and followed in general that described by Keown and others:¶ a polyethylene or polyvinylene tube was inserted into a convenient arm vein, and anesthesia was induced with thiopental (Pentothal) sodium through this tube. Procaine hydrochloride in concentrations of 0.2% to 0.5% (depending on the vigor of the patient) was started as a continuous intra-

¶ References 14 and 15.

venous drip through another vein. Decamethonium (Syncurine) bromide, 2 to 5 mg., was then given intravenously for relaxation of the jaw, and orotracheal intubation with cuffed tube was performed. The cuff was inflated immediately, and controlled respiration with 100% oxygen was started. When the color, the pulse, and the blood pressure of the patient were satisfactory, the anesthesia machine was set to deliver 2 to 3 liters of nitrous oxide and 1 liter of oxygen per minute. A circle filter connected directly to the endotracheal tube was used continuously, and the excess gas was allowed to escape at pressures varying from 5 to 15 mm. Hg, depending on the pressure necessary to adequately inflate the lungs. The procaine infusion was given throughout the operation at the maximum rate which did not depress the blood pressure. Controlled respiration was continued until the thorax was closed and as much air as possible had been expelled from the intrapleural space. Thiopental was added from time to time, but the patients were maintained in such a light state of anesthesia that they frequently moved slightly during the operation. Cyanotic and orthopedic patients were placed in a semisitting position on the operating table and were allowed to breathe 100% oxygen for 5 to 10 minutes prior to induction of anesthesia. All patients were anesthetized and intubated by the ultrarapid or "blitz" technique, and the time from the commencement of the administration of the thiopental to assumption of controlled respiration on 100% oxygen invariably was less than 90 seconds.

Patients were maintained during surgery as the immediate situation demanded and not according to a preset plan. If the heart rate became unduly slow, intravenous atropine was given; if the force of cardiac contraction seemed to be failing, lanotoside C (Cedilanid) was given intravenously. When a large blood loss was anticipated (as in aortic commissurotomy by the transventricular approach with the Bailey Aortic Dilator) or when blood loss became pronounced, blood was administered. Intravenous calcium chloride was used empirically,[6] but particularly when cardiac difficulties developed during or after the administration of blood.

Blood pressure depression occurred frequently in these patients during surgery. Tachycardia did not usually accompany it, nor was the pallor and the cold wet sweat of shock commonly seen with it. These were eliminated in part by the continuous intravenous procaine infusion, but the probability that the intracardiac manipulations incident to surgery may have produced this decrease in blood pressure must also be considered. Blood pressure depression was judged on the basis of the preoperative blood pressure level and as a general rule was treated whenever the systolic pressure fell below 80 mm. Hg, or 20 points below the preoperative level in those cases in which the preoperative level was 80 mm. Hg or less. Hypertensive patients were judged to have suffered a proportional fall in blood pressure at higher levels.

In the absence of unusual hemorrhage, which was treated by blood transfusion, blood pressure depression was managed with vasopressors.

The two drugs used as vasopressors were levarterenol and methoxamine (Vasoxyl). Epinephrine was used in only a few cases after one or both of the above vasopressors had failed, but the number of cases was so small that no opinion as to its relative efficacy could be formed.

The selected vasopressor was added to 5% dextrose in water and infused intravenously. The rate of infusion was regulated in as close to minute-to-minute fashion as possible in order to maintain the blood pressure at the desired optimum level. Ordinarily 40 mg. of methoxamine was added to 500 cc. of dextrose in water, or 4 mg. of levarterenol was added to 800 to 1000 cc. of the same. The concentrations of the vasopressor drugs were increased either initially, after the infusion had been started, or when the volume of fluid being given seemed to be too great for the individual patient.

There were 224 cases of cardiac and intra-

TABLE 1.—*Two Hundred Twenty-Four Cases of Cardiac and Intrathoracic Great Vessel Surgery*

	No. of Patients	Died in OR*	Died in Hospital but After OR*
A. Type of operation			
Extracardiac, intrapleural	11	0	1
Intracardiac	213	11	30
Total	224	11	31
B. Use of vasopressor drugs			
None	107	5	12
Levarterenol or methoxamine	117	6	19
Total	224	11	31
C. Methoxamine alone	21	0	0
Methoxamine failed, then levarterenol	10	2	3
Levarterenol	86	4	16
Total	117	6	19

* OR indicates operating room.

thoracic great vessel surgery in this series (Table 1, B). Of these, 107 did not suffer blood pressure depression and received no vasopressor during surgery. Of these 107 patients (Table 1, B), the 8 subjected to great vessel surgery all lived through the operation, but 1 undergoing the Bailey-Beck operation for coronary insufficiency died later of renal failure; of the remaining 99 who were subjected to intracardiac surgery, 5 died in the operating room, and 11 died later while still in the hospital. The causes of death in those who died during the operation make obvious the reason that no vasopressor was used: two deaths occurred from surgical technical difficulties, one from anesthetic technical difficulties, one from uncontrollable hemorrhage, and one from cardiac failure. This last patient was one in whom 75% of a severe mitral regurgitation was eliminated by surgical correction. The heart seemed unable to adjust to this sudden change in hemodynamics, and the patient died during the fourth attack of ventricular fibrillation.

In 117 of the patients (Table 1, C) one or more vasopressor agents were given during surgery. In 31 of this group methoxamine was used as the first vasopressor with the following results. The blood pressure rose to satisfactory levels in 12 cases, was not changed appreciably in 7 cases, dropped even lower after the methoxamine infusion in two cases, and failed to respond so that levarterenol was given in 10 cases. In two of the 12 cases in which a satisfactory level of blood pressure appeared after administration of methoxamine, the patients had no detectable blood pressure before the drug was given, but in the other 10 patients the situation was not so precarious. None of these 21 patients died in the operating room. In the 10 additional patients in whom methoxamine failed to raise the blood pressure and levarterenol was then given, levarterenol raised the blood pressure to some extent in each case. Of these 10 patients, 2 died during surgery—one from a cerebral embolus and the other from uncontrollable hemorrhage during an attempt at mitral suture for correction of mitral insufficiency. Three others died prior to discharge from the hospital.

In the remaining 86 cases, levarterenol was used as the original chosen vasopressor. These 86 cases have been grouped together with the 10 cases in which levarterenol was used after methoxamine had failed, making a total of 96 cases in which levarterenol was used during cardiac surgery. These 96 cases are treated as a single group in Table 2 and after; they consisted of 2 extracardiac and 94 intracardiac operations.

TABLE 2.—*Need for and Effect of Levarterenol During Operation by Age of Patient*

Age in Years	Number of Patients			
	No Levarterenol	Blood Pressure Raised from Zero	Blood Pressure Raised	Total
0–9	1	0	0	1
10–19	9	0	1	10
20–29	24	6	10	40
30–39	42	7	20	69
40–49	48	14	25	87
50–59	4	6	5	15
60–69	0	0	2	2
Totals	128	33	63	224

We have distinguished between those patients receiving levarterenol in whom the blood pressure had apparently fallen to zero and those patients in whom the drug was used when the blood pressure had not completely disappeared prior to its use. This

TABLE 3.—*Need for, and Effect of Levarterenol During Operation by Type of Operation*

Operations*	Number of Patients			
	No. Levarterenol	Levarterenol Raised BP from Zero	Levarterenol Raised BP	Total
MC	93	21	45	159
MC-MS	3	3	3	9
MC-AC-TC	0	1	0	1
AC	9	2	7	18
MS	3	1	2	6
AC-MC	4	4	0	8
MC and lobectomy	0	1	0	1
Bailey-Beck	2	0	1	3
MC and aortic peduncle	0	0	1	1
AC and aortic peduncle	1	0	1	2
Aortic peduncle	0	0	1	1
Brock valvulotomy	1	0	1	2
Poudrage	1	0	1	2
TC	1	0	0	1
Atrioseptopexy	1	0	0	1
Exploratory cardiotomy	2	0	0	2
Wineberg	1	0	0	1
Excision patent ductus art.	2	0	0	2
Resection and anastomosis, aorta for coarctation	1	0	0	1
Excision pericardial cyst	2	0	0	2
MC-TC	1	0	0	1
Totals	128	33	63	224

* Glossary of abbreviations:
MC, mitral commissurotomy for mitral stenosis.
AC, aortic commissurotomy for aortic stenosis.
MS, mitral suture for mitral insufficiency.
TC, tricuspid commissurotomy for tricuspid stenosis.
Bailey-Beck, a piece of subclavian artery is used to connect the coronary sinus to the aorta in arterialization of the coronary sinus for coronary insufficiency.
Poudrage, asbestos is inserted into the pericardium for coronary insufficiency.
Aortic peduncle, a conical-shaped solid mass of nylon cloth is sutured by its tail to the left ventricular wall, while the mass of the cone lies in the aorta to correct aortic insufficiency.
Brock valvulotomy, for relief of pure pulmonary stenosis.
BP, blood pressure.
OR, operating room.

TABLE 4.—*Types of Operation by Age Groups in Which Levarterenol Raised the Blood Pressure from Zero*

Operations*	Number of Patients, by Age Groups						
	0–9	10–19	20–29	30–39	40–49	50–59	Totals
MC	0	0	3	4	10	4	21
MC-MS	0	0	1	1	1	0	3
MC-AC-TC	0	0	1	0	0	0	1
AC	0	0	0	1	0	1	2
MS	0	0	0	0	0	1	1
AC-MC	0	0	0	1	3	0	4
MC and lobectomy	0	0	1	0	0	0	1
Totals	0	0	6	7	14	6	33

* For Glossary of Abbreviations, see footnotes to Table 3.

has been done because there is a real difference in the concern rightly felt by the team between these two grades of difficulty during surgery. Table 2 shows how many patients in each age group required levarterenol during the operation.

Table 3 shows the type of operation and the effect of levarterenol on these patients. Table 4 shows the age distribution by type of operation of the cases in which levarterenol raised the blood pressure from zero, and Table 5 shows the amount of maximum rise following administration of the drug in these cases. In only one case in which the blood pressure had fallen to zero did it fail to rise at least 60 points after intravenous infusion of levarterenol; this patient suffered a cerebral embolus during mitral commissurotomy, and ultimately all other resuscitative measures failed also. In Tables 6 and 7 those cases receiving levarterenol in which the blood pressure had not disappeared completely are similarly separated by age and type of surgery. Blood pressure elevation was noted, at least temporarily, in every case in this group.

There were six deaths in the operating room among patients given levarterenol for low or absent blood pressure. Two of these had received methoxamine before the administration of levarterenol, as has been described previously. The causes of death in the other four cases were hemorrhage in two instances and ventricular fibrillation in the other two. Three of these four deaths occurred in patients with aortic stenosis in whom aortic commissurotomy was being attempted. The fourth was a severe case of mitral insufficiency in which mitral suturing was tried. All had exceptionally poor cardiac function preoperatively, and one had been previously refused by us for surgery. Sixteen other patients died prior to discharge from the hospital.

The following case is illustrative of the over-all experience with levarterenol.

Report of a Case

A 43-year-old white woman was admitted on Dec. 1, 1953, with the classical findings of severe mitral stenosis and incipient congestive heart failure, indicated by rales at the base of the right lung. Her blood pressure was 115/70. Laboratory studies showed a trace of albumin in the urine, a corrected sedimentation rate of 27 mm. in one hour, a total plasma protein of 5.45 gm./100 cc. with a normal

TABLE 5.—*Type of Operation and Amount of Systolic Blood Pressure Rise from Zero with Levarterenol*

Operation*	No. of Patients, BP Rise from Zero After Infusion of Levarterenol in Mm. Hg of rise by operations‡					
	to 0	60	100	120	Over 120	Totals
MC	1	2	5	6	7	21
MC-MS	0	1	1	0	1	3
MC-AC-TC	0	1	0	0	0	1
AC	0	0	0	2	0	2
MS	0	0	0	1	0	1
AC-MC	0	0	0	2	2	4
MC and lobectomy	0	0	0	0	1	1
Totals	1	4	6	11	11	33

* For Glossary of Abbreviations, see footnotes to Table 3.

TABLE 6.—*Type of Operation and Amount of Systolic Blood Pressure Rise with Levarterenol —Cases in Which the Blood Pressure Was Not Zero Before Levarterenol*

Operation*	No. of Patients, Systolic Blood Pressure Rise in Mm. Hg										
	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100–109	100 or More
MC	1	3	3	11	8	2	5	4	5	1	2
MC-MS	0	1	0	0	0	1	1	0	0	0	0
MC-AC-TC	None										
AC	2	0	0	0	1	1	0	3	0	0	0
MS	0	1	0	1	0	0	0	0	0	0	0
AC-MC	None										
Bailey-Beck	0	0	0	0	1	0	0	0	0	0	0
MC and aortic peduncle	0	0	0	0	0	0	0	1	0	0	0
AC and aortic peduncle	0	0	1	0	0	0	0	0	0	0	0
Aortic peduncle	0	0	0	0	0	0	0	0	0	1	0
Brock valvulotomy	0	0	0	0	1	0	0	0	0	0	0
Poudrage	0	0	0	1	0	0	0	0	0	0	0
Totals	3	5	4	13	11	4	6	8	5	2	2

Grand total in which levarterenol was used when BP was not zero is 63.
* For Glossary of Abbreviations, see footnotes to Table 3.

TABLE 7.—*Type of Operation by Age Group—Cases in Which the Blood Pressure Was Not Zero Before Levarterenol*

Operation*	No. of Patients, by Age Groups							
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	Totals
MC	0	0	4	17	19	4	1	45
MC-MS	0	0	2	1	0	0	0	3
MC-AC-TC	None							
AC	0	0	1	1	4	1	0	7
MS	0	1	1	0	0	0	0	2
AC-MC	None							
Bailey-Beck	0	0	0	0	1	0	0	1
MC and aortic peduncle	0	0	1	0	0	0	0	1
AC and aortic peduncle	0	0	0	0	1	0	0	1
Aortic peduncle	0	0	0	1	0	0	0	1
Brock valvulotomy	0	0	1	0	0	0	0	1
Poudrage	0	0	0	0	0	0	1	1
Totals	0	1	10	20	25	5	2	63

* For Glossary of Abbreviations, see footnotes to Table 3.

A/G ratio and a prothrombin time 71% of normal. All other studies were within normal limits.

Under adequate preoperative treatment the rales disappeared by Dec. 5, 1953, and the patient was brought to the operating room at 11 A.M. on this date. Her blood pressure was 100/60, pulse 66, and respirations 20. Anesthesia was started at 11:05 A.M., preparation was completed, and surgery was begun at 11:20 A.M.

At 12:02 P.M., while the mitral valve was being explored, the blood pressure and pulse suddenly disappeared, although the heart continued to beat. An amount of 4 mg. (4 cc.) of levarterenol was added to 800 cc. of 5% dextrose in water, and the

mixture was infused intravenously. The blood pressure almost immediately reappeared at 100/70 and rose to 160/110. The infusion was slowed until the systolic pressure settled back to 100. After the anterior and posterior mitral commissures had been cut, the blood pressure was 70/50. The rate of levarterenol infusion was increased, and the blood pressure rose to 115/75 with a pulse rate of 80 to 100 per minute, which was maintained without difficulty until the completion of the operation at 12:50 P.M. The patient left the operating table awake and in good condition. She had received a total of 100 cc. of 0.2% procaine and 125 cc. of 0.5% thiopental with nitrous oxide oxygen under continuous controlled respiration. The levarterenol infusion was continued at a decreasing rate until the blood pressure remained stable at satisfactory levels without it. Her convalescence was uneventful.

Comment

It should be understood that this is not a controlled study in any sense. Some of the operations here reported had never been done on a human being before. Many of them presented such a challenge that the primary concern of the whole surgical team was getting the patient through the operation alive. While this is the primary concern of every anesthesiologist and surgeon in every operation, it becomes much more prominent during cardiac surgery, as all who have been involved in it will understand. The graphic records kept as accurately as possible during the surgery form the basis of the data for this report.

Many more patients received levarterenol than methoxamine in the early part of this series because of the previous experience of one of us (J.E.R.) with both drugs.# The experience of this study, particularly of the 10 patients who failed to respond to methoxamine but who did respond to levarterenol, suggested further that the latter was the more efficacious vasopressor agent for use in cardiac and great vessel surgery.

Recent laboratory work on the dog is of interest in that it demonstrates a beneficial action on the heart itself by levarterenol which methoxamine lacks. Brewster and co-workers [7] have shown that levarterenol exerts a positive inotropic effect on the myocardium, increasing cardiac output in the dog under ether anesthesia. Jamison and co-workers [8] have shown that levarterenol increases the coronary blood flow by its coronary vasodilator action in the dog under thiopental anesthesia out of all proportion to the rise in blood pressure produced. In their studies, both Brewster and Jamison found that the action of epinephrine was similar to and comparable in effect to levarterenol.

Reasoning from the armchair, one must question the logic of using methoxamine during cardiac surgery. The drug is a pure peripheral vasoconstrictor with no cardiac effects other than reflex.* In those cases in which blood pressure fall is due to a failing heart, it would seem unwise to raise the peripheral resistance against which the failing pump is working, since this might further embarrass it and tend to increase the severity of the cardiac failure.

When the level of the blood pressure rises during cardiac surgery from infusing methoxamine, it can be regulated with relative ease, since the blood pressure changes are not sudden either in elevation or depression. This is not so with levarterenol, and one cannot overemphasize the importance of almost continuous blood pressure determinations to permit adjustments of the levarterenol infusion rate in accordance with the blood pressure changes. The evanescent action of the drug makes these precautions necessary whenever it is used on any patient. They are even more important to remember during cardiac surgery, because of the rapidly changing status of the heart's action. The manipulations incident to surgery, the corrective surgery itself, the frequency of alterations in rhythm during surgery, and the abnormal condition of the heart which required the surgery to be performed all contribute to this rapidly chang-

References 1 and 10.

* References 9 and 10, and Fassett, D. W., and Taube, H.: Unpublished data cited in a summary of Therapeutic and Clinical Notes on "Vasoxyl," Tuckahoe, N. Y., Burroughs Wellcome & Company, Inc.

ing cardiac status, which is peculiar to cardiac and great vessel surgery.

The value of levarterenol in shock due to myocardial infarction and trauma has been well demonstrated and is familiar to all who are interested in this subject.† The literature relating to its place in cardiac and great vessel surgery is not voluminous but is unanimous in the opinion that levarterenol is of value. Lief,[2] Black and Harken,[3] and Ridley and Pender [4] believe, as do we, that it should be used when indicated. Kepes and co-workers [5] routinely employ levarterenol from the commencement of surgery to maintain blood pressure at the desired level.

Summary and Conclusions

The incidence of blood pressure depression and/or shock as it occurred in 224 operations for the correction of intracardiac and intrathoracic great vessel abnormalities has been presented. The preanesthetic and anesthetic management has been outlined sufficiently to give the reader a basis for evaluation.

In 117 of the 224 patients, a vasopressor agent was administered for the regulation of the blood pressure. The results with methoxamine (Vasoxyl) and levarterenol (Levophed), also known as norepinephrine, are presented, and the conclusion is drawn, on the basis of the data presented, that levarterenol is at this time the vasopressor of choice for the management of blood pressure depression during cardiac and great vessel surgery. In 95 of 96 patients, the blood pressure rose significantly after its administration.

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Carcinoma of the Large Bowel with Metastasis to the Genitalia

Report of Two Cases

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In this communication we will present briefly two unusual cases, one a man and one a woman, then proceed with theoretical considerations in regard to possible mechanisms of spread of malignant cells in the areas involved, and, finally, consider practical aspects of diagnosis and management.

Metastatic carcinoma of the penis from all sites is very rare. In 1944, Wattenberg [1] reviewed the literature and collected only 20 cases which originated in the prostate, kidney, testis, liver, rectum, or bladder. In 1954, Poutasse [2] found 32 cases of metastasis to the penis in the literature. Of these the original source was as follows: prostate, 11; urinary bladder, 6; rectum, 6; testis, kidneys, lungs, liver, and ilium, 9. Poutasse added two more cases of carcinoma of the bladder and two cases of carcinoma of the rectum with penile metastasis. This brought the number of cases of carcinoma of the rectum with this type of metastasis to eight.

Ney [3] in 1952 found seven similar cases in the literature and added one case of his own, also making a total of eight. Eight cases is the largest number that has been recorded in any report to date. We were able to collect 12 cases from the literature, and, with one additional of our own, we now have a total of 13. We have not been able to find a report similar to our second case of metastasis from the large bowel to the genitalia in the female.

Table 1 shows some interesting data concerning the reported cases. Age range is from 30 to 72. Priapism was the presenting symptom in 3 of the 12 cases. Abdominoperineal resection was done prior to discovery of the metastasis in six cases. A colostomy was done in four cases, two before the metastasis was noted and two at the same time. There was no bowel surgery in two cases.

TABLE 1.—*Carcinoma of Rectum With Metastasis to Penis Summary of Reported Cases*

Patients (Age Range, 30-72)	12
Abdominoperineal resection	6
Colostomy	4
No bowel surgery	2
Primary lesion removed before metastasis known	8
After treatment of metastasis	
5 died within 10 mo.	
1 living at end of 1 ½ yr.	
1 living at end of 9 yr. (local excision)	
1 no follow-up	
Primary lesion and metastasis detected at same time.	4
All died within 5 mo.	

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In Table 2 analysis of the reported cases is given in more detail.

The primary lesion was removed before the metastasis was known in eight cases. After treatment of the metastasis, five died within 10 months, one was living at the end of 1½ years, one living at the end of 9 years, and in one there was no follow-up.

Of the four cases in the literature in which the primary lesion and metastasis were detected at the same time, none lived more than five months. The primary lesion and the metastasis were discovered at the same time in the man whose case is given in our report. He lived two years and eight months after operation. In the case of the woman the metastasis was found first and led to discovery of the primary carcinoma. She lived 3 years after removal of the metastasis and 2 years and 10 months after excision of the primary carcinoma of the sigmoid.

Report of Cases

A 62-year-old unmarried post office inspector was admitted to the hospital on Jan. 31, 1951, with a chief complaint of a rash on his legs for about one year's duration. About six weeks prior to admission the rash became widespread and itching was intense on his right leg. He had lost about 7 to 8 lb. in weight; otherwise, he felt well.

For about nine years he had had symptoms suggestive of intermittent claudication. During the few weeks prior to admission he had mild anorexia. He had noted smaller caliber of stools but denied any diarrhea, constipation, tenesmus, or rectal bleeding. There were no genitourinary symptoms. Family history was noncontributory.

Physical examination revealed a well-developed,

TABLE 2.—*Analysis of Reported Cases*

	Author	Patient's Age, Yr.	Chief Complaint	Treatment	Survival	
					After Bowel Operation	After Metastasis Operation
1.	Niewiesch [4]	69	Priapism	Previous resection of rectum for adenocarcinoma; amputation of penis	2 yr. 4 mo. after combined abdominoperineal resection	10 mo. after amputation of penis
2.	Mathesan [5]	72	Urinary retention	Colostomy one month prior to urinary retention	5 mo.	None
3.	Stein and Hantsch [6]	62	Priapism Diarrhea, 14 mo.	Refused surgery; dead in 3 mo.	None	None
4.	Kerr and Gillies [7]	60	Dysuria, 3 mo.	Resection of rectum	3 yr. (living)	Amputation (no follow-up)
5.	Melicow and Ganem [8]	—	--------	Colostomy (liver metastasis)	9 mo.	2 mo.
6.	Thompson [9]	70	Urinary retention and rectal pain	Suprapubic cystostomy 3200-r x-ray therapy; dead in 4 mo.	None	None
7.	Cattell and Mace [10]	30	Priapism 2½ yr. after abdominoperineal resection	Adominoperineal resection; excision of proximal left corpus cavernosum and a section of right corpus cavernosum	11 yr. 5 mo. after rectal operation	9 yr. (living)
8.	Ney [3]	52	Constipation, melena, dysuria; (Postoperatively) increased	Combined abdominoperineal resection, 1944	5 yr.	4 mo.
9.	Bowersox & Frerichs [11]	68	Constipation, melena, nocturia	Colostomy	2 mo.	None
10.	Poutasse [2] (two cases)		(*a*) Dysuria	Combined Abdominoperineal resection; amputation, penis	18 mo.	4 mo.
			(*b*) Dysuria	Colostomy; biopsy of penis	6 mo.	5 mo. (biopsy)
11.	Boyd [12]	54	Weight loss; rectal bleeding; small caliber stools; burning; nocturia; decrease in size of urinary stream	Combined abdominoperineal resection, 1945; local penile resection, 1951; radical amputation, 1952.	7 yr. (living)	1¼ yr. (living)

well-nourished man in no distress. Blood pressure was 140/70. The skin on the left leg revealed a scaling erythema with papules and similar lesions on the right leg, which were more intense and confluent. There was some enlargement of the left inguinal nodes. Genitalia showed a penile ulceration on the dorsum of the glans penis 3 to 4 mm. in diameter, with surrounding induration which was suggestive of a syphilitic chancre. He had moderate-size varicose veins of both legs. No main vessel pulsations below the femorals, bilaterally, were felt.

Rectal examination revealed just within the external sphincter an annular, irregular, hard, movable constricted mass through which the fifth finger could pass only with some difficulty (Fig. 1).

Fig. 1.—Carcinoma of the rectum. Gross specimen from a man. Constriction of the lumen of the bowel from the growth may be seen just above the mucocutaneous junction.

Laboratory examination showed a hemoglobin level of 15.2 gm. and a normal white blood cell count. Dark-field examination of the penile lesion was negative on two successive occasions. Stool specimen was guaiac-positive. Hinton test was negative. Biopsy of the rectal mass showed invasive carcinoma. Biopsy of the penile lesion showed adenocarcinoma. Chest film was negative. There was no evidence of other metastatic disease.

A combined abdominoperineal resection and local excision of the penile metastasis was carried out. At operation there was no evidence of pelvic or periaortic lymph node or other organ metastases. Involvement of the levator ani could be made out during operation.

Pathological report was as follows: (1) adenocarcinoma of rectum, extension through muscularis, extension into blood vessels and lymphatics; (2) metastasis to erectile tissue of penis (Fig. 2); (3) no evidence of malignancy in six lymph nodes, and (4) perineural and perivascular mesenteric lymphatic invasion. Diagnosis—mucus-producing adenocarcinoma, metastatic to erectile tissue of penis; ulceration over tumor.

The abdominal, perineal, and penile wounds healed well, and the colostomy functioned in a satisfactory manner. The patient was discharged on the 22nd postoperative day. During the next two years eight months, he was gainfully occupied at his regular position about half the time.

He was readmitted to the hospital during the next two and one-half years on four occasions—a total of 43 days—for (1) ligation of varicose veins to control the pruritus (2) reexcision of the penile ulcer (3) simple amputation of the penis and excision of recurrent nodule, posterior wound, and (4) treatment of recurrent lower-extremity pruritus, which was his only cause of discomfort. Two months before his death he developed an enlarged liver and jaundice. He was up and about until 10 days before his death, which occurred in October, 1953.

This case represents the second longest known survivor of the series after discovery of the metastasis. The case of Cattell and Mace[10] was living at the time of their report in 1951, eleven years and five months after combined abdominoperineal resection and nine years after local excision of penile metastasis. He is an extraordinary case and may represent one of those very rare instances in which a solitary distant metastasis has been completely excised.

The second case is an analogous lesion in a woman. In August, 1947, this 52-year-old white married housewife complained of vaginal staining of two months' duration. Eight years previously, supravaginal hysterectomy was performed with no subsequent vaginal staining until the present episode.

A 1.5 cm. friable cauliflower growth was attached to the lateral vaginal wall midway between the cervix and the introitus. Biopsy showed adenocarcinoma. There was much speculation regarding the site of origin. The possibility of the primary carcinoma being left behind in some retained endometrium at the time of hysterectomy was entertained. Biopsy of the cervix were negative. It was finally decided this must be a rare primary adenocarcinoma of the vagina. The gastrointestinal tract was not considered as a primary site.

In October, 1947, cervicectomy and excision of

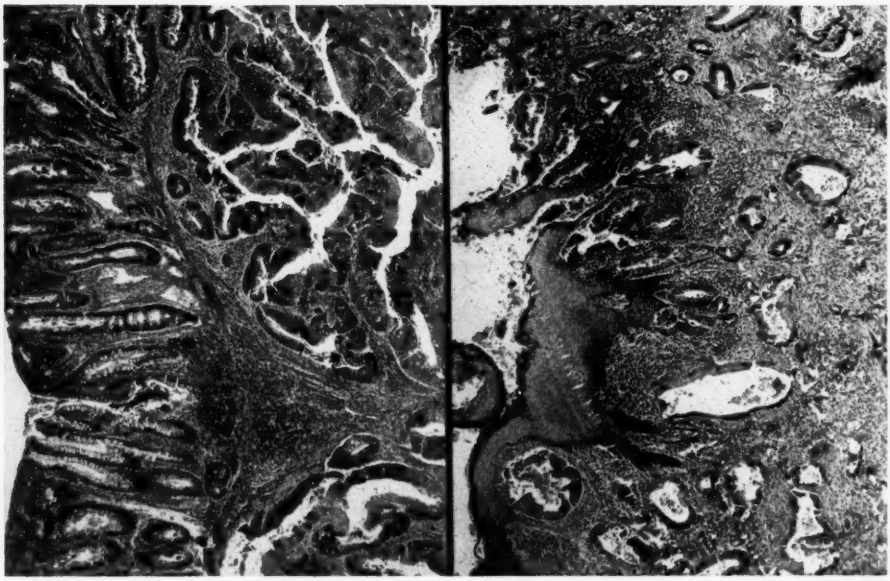

Fig. 2.—Carcinoma of the rectum with metastasis to the penis. Microscopic appearance of the primary lesion is shown on the left side and the metastatic lesion on the right side of the illustration.

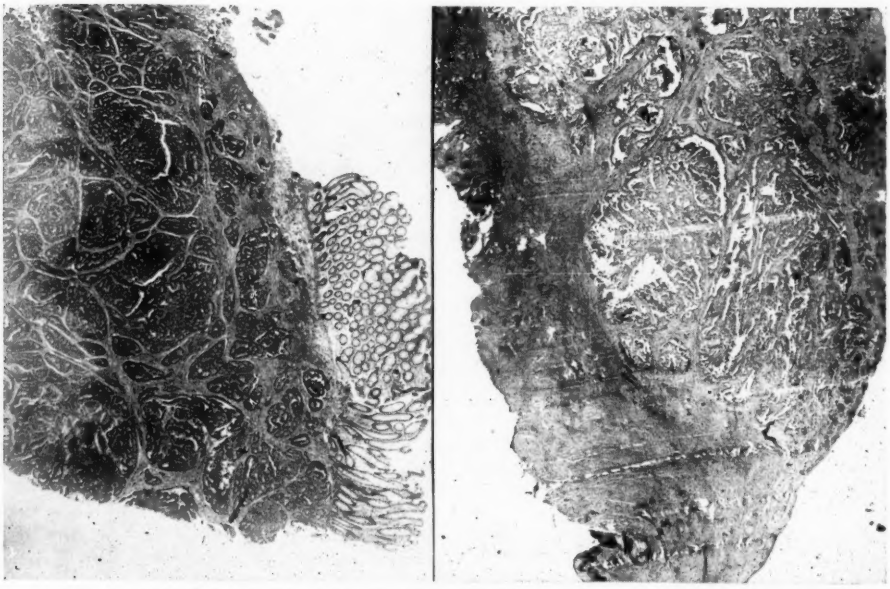

Fig. 3.—Metastasis of adenocarcinoma from sigmoid to vagina (low power). The primary lesion is shown on the left side and the metastatic lesion on the right side of the illustration. (Note vaginal epithelium at left lower corner.)

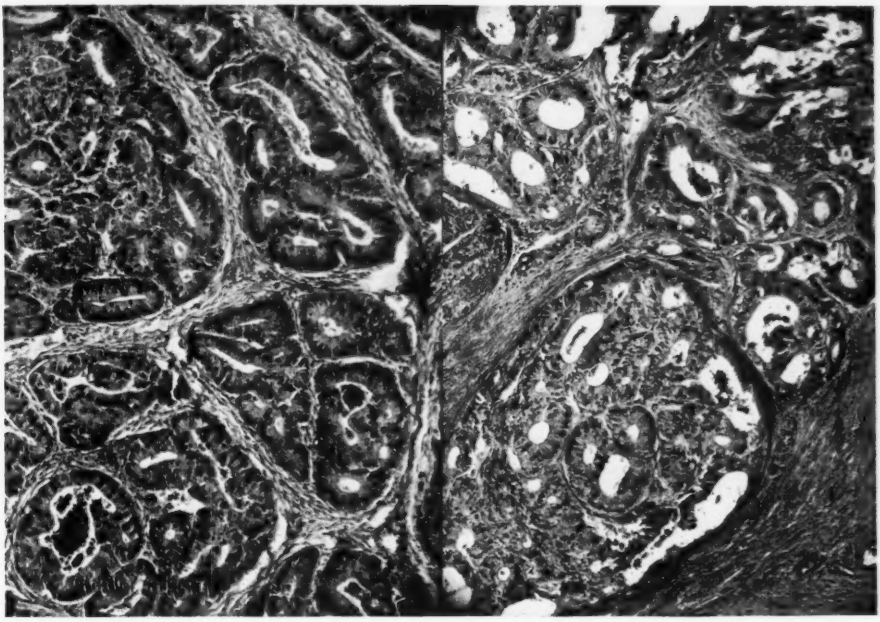

Fig. 4.—Metastasis of adenocarcinoma from sigmoid to vagina (high power). The primary lesion is shown on the left side and the metastic lesion on the right side of the illustration. (×95)

the vagina was carried out. Radium treatment was also given during this admission. The pathologist, Dr. Shields Warren, suggested that the origin of the tumor might be in the gastrointestinal tract from the microscopic appearance (Figs. 3 and 4). Barium enema was done and a constricting lesion of the sigmoid seen. This did not have the appearance of malignancy but did resemble diverticulitis. In December, 1947, a carcinoma of the midsigmoid was resected. Recovery was uneventful. In January, 1948, radium was implanted in a tumor mass on the right side of the urethra. X-ray therapy was also given. In March, 1949, radium was implanted in the urethra. In May, 1949, no residual disease was found and no genitourinary symptoms. Bowels were regular. There was questionable enlargement of the liver at that time. In October, 1950, the patient died, three years three months after initial symptoms.

Theoretical Considerations

There are three possible routes of metastatic spread which have to be considered: (1) direct extension, (2) retrograde extension through lymph channels, and (3) extension through the blood stream. Which of these is most likely has been the source of speculation by almost every author who has written on this subject. Some have dismissed the subject by saying the method of metastasis might be by direct extension or retrograde lymphatic dissemination. Stein and Hantsch [6] stated that metastasis from the bowel to the genitalia could not be explained on a vascular or lymphatic basis. They believed the only logical explanation was that of the secondary involvement resulting from direct extension by way of the ischiorectal fossa, then, through the junction of the deep and superficial triangular ligaments with the fascia of Colles and into the superficial perineal space. This would be the course of less resistance, and the cells would not thereby spread against fascial planes. Ney [3] also entertained this explanation for the metastatic process, although he was not entirely happy with it.

It would seem to us that direct extension is not a good explanation, for there are areas of no involvement between the pri-

mary lesion and the metastasis. In most of the cases involvement at the metastatic site was by isolated nodules rather than as a continuous sheet of malignant cells from the perineum. It would be difficult also to invoke this as a method of spread from more distant sites, such as higher in the bowel and the kidney.

The second method of spread to be considered is possible retrograde flow through the lymph channels. Connell and Rottino,[13] among others, have shown by definite pathological demonstration in serial sections extensive retrograde involvement of lymph channels and lymph nodes for significant distances below the primary lesion. One specimen showed retrograde extension for 6.4 cm. For this reason many authors, including Lahey[14] and Judd and Bellegie,[15] have pleaded for wider resections and have pointed out the disadvantages of sphincter-preserving operations for cancer of the rectum, particularly in lesions at or below the peritoneal reflection because of the increased incidence of recurrence seen. Wide excision should not be sacrificed in order to avoid abdominal colostomy.

Although it has been stated[6] that metastasis from the rectum to the penis could not be explained on a lymphatic basis, it is our belief that this is possible, because of the following anatomical considerations. The lymphatics from the anal canal accompany the middle and inferior hemorrhoidal arteries and end in the hypogastric nodes, whereas those from the rectum traverse the pararectal glands and pass to those nodes in the sigmoid mesocolon. These efferents terminate in the preaortic nodes, around the origin of the inferior mesenteric artery. Lymphatics of the perineum pass to the inguinal nodes. The lymphatics of the urethra and those of the glans penis terminate in the deep inguinal and external iliac nodes. Those of the membranous and prostatic portions of the urethra in the male and those of the whole urethra in the female pass to the hypogastric nodes; hence, there are several distinct possibilities in which lymphatic drainage from both areas, namely, bowel and genital region, interconnect and, hence, could conduct malignant cells theoretically in a retrograde fashion, provided the lymph stream were reversed by blockage or for other reasons. Boyd[12] subscribed to retrograde lymph spread as his best explanation for metastases in these instances. Though retrograde lymphatic spread does occur, as we know, this seems a rather farfetched explanation for these particular cases because of the distances involved.

We should like to turn now to the more likely explanation which appeals to us as fulfilling all the requirements for this type of metastasis in a logical fashion. This involves spread by the blood stream through the vertebral veins. Any argument for arterial spread would have to include presumption of patent foramen ovale, and, in addition, one would expect other, more widespread, metastases.

Batson,[16] Way,[17] Bowersox and Frerichs,[11] Poutasse,[12] Solnitsky,[18] and Willis,[19] all believe there is a good explanation for the metastatic route in these rare cases. This route is by retrograde spread through the veins according to Batson. As Willis[19] states, "Tumor invasion of the spermatic or ovarian veins, which of course is much more common from tumors of the left kidney than from those of the right, may be followed by retrograde tumor embolism of the pampiniform or ovarian plexus or the parametrial or vaginal veins, and the development of secondary growths in the spermatic cord, epididymis, paramentrium, vagina, or vulva." In 1940[16] and 1942,[20] Batson reemphasized the importance of the vertebral veins in the metastatic processes. He said: "The vertebral vein system consists of the epidural veins, the perivertebral veins, the veins of the thoraco-abdominal wall, the veins of the head and the veins of the walls of the blood vessels of the extremities. It is a set of valveless vessels which carries blood under low pressures. In the subcutaneous tissue the smaller vessels provide a continuous network permitting ready permeation. Around the

vertebral column, the vascular bed of the system is much larger than required by the parts in which it is found. It is a system which is constantly subject to arrest and reversals in the direction of the flow of blood. The vertebral vein system parallels, connects with and provides by-passes for the portal, the pulmonary and the caval system of veins and hence can provide in itself a pathway for the spread of disease between remote organs." Brown and Warren,[21] in studying 170 rectal carcinomas with complete postmortem findings, showed that only 1 case of 70 showing visceral metastasis failed to show local intravascular invasion, whereas 24 cases failed to show positive lymph nodes. They believed that "Sections of the primary growth in rectal carcinoma should be scrutinized carefully for invasion of capillaries or veins by tumor because intravascular tumor invasion frequently means visceral metastases and its absence, provided at least three sections from different parts of the growth are examined, nearly always rules out visceral metastases. Its efficiency in predicting visceral or bone metastases out-ranks that of neoplastic lymph nodes." We believe this mode of spread is the route through which the metastasis occurred in these cases.

Practical Aspects

Although metastasis of this nature would appear to be very rare from reports in the literature, as always it is probably commoner than the reports would indicate. Because of the infequency of cases of this type, perhaps it is rather fruitless to discuss practical aspects. Nevertheless, we have learned certain interesting points from these cases, as follows: (1) take a biopsy specimen of any genital nodule and, if adenocarcinoma is found, look for a bowel lesion; (2) investigate the gastrointestinal tract in cases of priapism, if explanation is obscure; (3) in patients with bowel carcinoma and urinary symptoms, search carefully for metastatic genital nodules preoperatively.

As far as management is concerned, we have drawn the following conclusions from studying these cases: (1) For palliative treatment, radical operation of the primary lesion may be justified in certain cases; (2) locally excise metastatic penile nodules when possible; otherwise, simply amputate the penis; (3) in all cases of cancer surgery observe the standard dictum and minimize manipulation of the primary lesion before or during operation and ligate venous and lymph drainage as early as possible; (4) in adenocarcinoma of the vulva or vagina the gastrointestinal tract must be included in the study for location of primary disease before extensive pelvic surgery for eradication of a possible hidden focus is undertaken.

Summary

Two unusual cases of metastatic adenocarcinoma from the large bowel to the genitalia have been described. Various interesting implications, both as regards the route of metastatic spread and the diagnosis and prognosis, have been discussed.

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Perforation of Duodenal Ulcer and Rupture of Stomach

Report of Two Cases in Newborn Infants with Survival Following Closure

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According to the reported cases, perforation of a peptic ulcer and rupture of the stomach are rare entities in infancy, inasmuch as only 30 such cases have been reported up until the end of 1954.[1]

Peptic ulceration in infants and children, including perforation, was reviewed by Holt in 1913. Bird, Limper, and Mayer reported[2] 33 cases of perforation in a total of 245 cases of peptic ulcer in infants and children from 17 days to 15 years of age. Other summaries are those of Guthrie,[3] Hollander and Stark,[4] McAleese and Sieber,[5] and Hutchins.[6] The earliest perforated peptic ulcer in infancy to be treated surgically with recovery was that in a 34½-hour-old baby reported by Bird and co-workers.[2] Lee and Wells described[9] a perforation of an ulcer in utero and numerous authors have reported perforations of duodenal ulcers in infants in the first few days of life.

Leger and associates[7] were apparently the first to close a perforation of the stomach in a 6-day-old infant, in 1950. Kellogg and his co-workers reported a second[8] and Northway and associates a third infant surviving perforation of the stomach after surgical closure.[12]

Etiology

The earliest cases of perforation of the stomach were found to be due largely to peptic ulcer, as reviewed by Thelander and Mathes in 1939.[10] A congenital defect in the musculature of the stomach as another cause of perforation was first described in 1943 by Herbert.[11] A third possible factor in perforation is the existence of other defects, such as atresia at the pylorus or in the duodenum, together with subsequent dilatation of the stomach. Other mentioned causes for perforation of the stomach in infancy are injury due to gavage feedings, neonatal asphyxia, embolism, thrombosis, vascular disease, and sepsis.

Peptic ulceration in infancy has been observed more commonly after difficult labor with evidence of intracranial damage or new growths, as pointed out by Vonderahe,[15] Cushing,[16] and Miller.[17]

Of the cases herein reported, the first was a duodenal ulcer in an infant in whom no evidence of any intracranial disease was manifest and the second was due to a spontaneous congenital weakness in the greater curvature of the stomach.

Pathology

Perforations from ulcers may occur in either the duodenum or the stomach, but rupture due to congenital muscular defects usually occurs along the greater curvature. In the latter case rents up to 2.5 cm. in length have been observed. Ulcers may vary in size from a few millimeters to 1.5 cm. and may be multiple.[2] In the newborn infant ulcers are always acute, and, since they occur rapidly, there is usually no evidence of acute inflammatory reaction adjacent to the perforation. However, necrosis and hemorrhage do occur, as pointed out by Fosmon and co-workers.[18]

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From the Homer G. Phillips Hospital.

Clinical Manifestations

Diagnosis of perforation is usually never made at the bedside, inasmuch as the signs and symptoms merely indicate some severe intra-abdominal disease. The infants usually eat poorly and frequently regurgitate and may show blood in the stools or hematemesis. Pallor, lethargy, abdominal distention, and peripheral circulatory impairment should also suggest an acute perforation. Although the abdomen on palpation may be relatively soft, it can show unusual tympany on percussion and evidence of intra-abdominal fluid. Fever and leucocytosis are usually absent, but anemia may be prominent if bleeding has occurred.

The diagnosis is usually made with the help of the radiological examination, which shows pneumoperitoneum. In the two cases herein presented, the x-ray picture led immediately to operation, after which the diagnosis was obvious.

Treatment

Perforation is an exclusively surgical problem, inasmuch as the spontaneous sealing off of the opening with eventual recovery has not been demonstrated to occur, at least as far as is known. Although emergency surgery is necessary, general supportive measures, such as transfusions, chemotherapy, and correction of dehydration, are important but can usually be carried out at the same time as operation, which should never be postponed unduly.

Case 1.—A 3 lb. 12 oz. male infant was delivered spontaneously by an eclamptic mother on May 13, 1952.

Physical examination revealed a premature, somewhat lethargic infant, but with a good pink color, even and regular respirations, and a weak cry. There was evidence of congenital heart disease. Two days after birth the abdomen was found to be tightly distended and tympanitic, and the baby vomited brownish material on two occasions. The rectal ampulla was empty, and a small dark-brownish stool was passed, which showed a positive guaiac reaction. The next day the infant was dehydrated and the abdomen was still distended and tympanitic. A left inguinal hernia was distended with gas. There were no stools, and the baby vomited again—coffee-ground-like material. Radiography of the abdomen taken in the upright position revealed a large collection of gas between the liver and the right diaphragm. There was also unusual gaseous distention of the intestines, both large and small. The radiological diagnosis was perforation of a hollow viscus and paralytic ileus

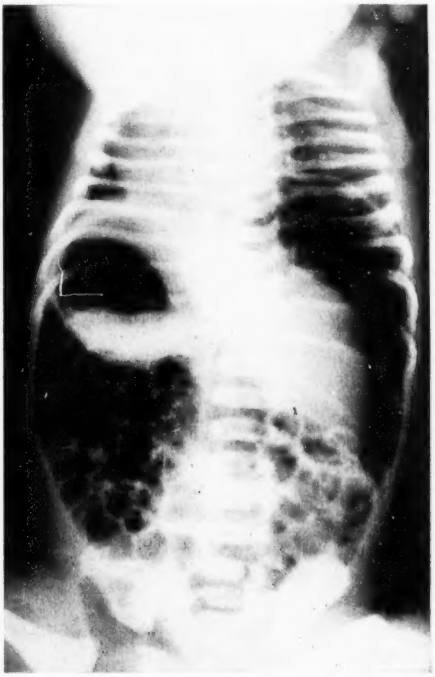

Fig. 1.—Flat plate and upright x-ray film of abdomen revealing pneumoperitoneum.

(Fig. 1). Operation was carried out soon afterward with local ½% procaine hydrochloride (Novocain) anesthesia. The abdomen was entered through a midline incision, and bloody fluid and clots were evacuated from the peritoneum. The stomach was adherent by fibrinous adhesions to the anterior surface of the liver. When these adhesions were gently separated, a perforation was noted in the anterior surface of the first part of the duodenum just distal to the pylorus. The edges were not friable or indurated. The opening was closed transversely by interrupted 00000 black nonabsorbable surgical (silk) inverting sutures. The abdomen was then closed in layers.

The baby did well after operation but three days later developed edema in both feet and slight anemia, both of which responded to whole-blood transfusions. Thereafter the course was uneventful. One month later upper gastrointestinal series revealed a spastic duodenum and lower gastroin-

testinal series congenital malformation, redundant sigmoid, and incomplete rotation of the cecum. The patient was discharged well on July 5, 1952, and was developing normally when last seen, in August, 1955.

CASE B.—A male infant was born uneventfully on Aug. 29, 1952. Two days later he started to vomit bile-stained material but had passed meconium stools since birth. On physical examination the infant was in a fair state of nutrition, lying quietly in bed but spasmodically whimpering and crying. The abdomen was distended and tympanitic. Bowel sounds were not heard and peristalsis was not visible. The urine showed a trace of sugar, 1+ albumin and 4+ acetone. White blood cells were 7000, red blood cells 4,600,000, with a hemoglobin of 16 gm./100 cc. The stools were positive for occult blood. An x-ray of the abdomen showed pneumoperitoneum (Fig. 2). The patient was operated upon immediately with procaine hydrochloride intercostal block anesthesia. When the peritoneum was opened, 50 cc. of serous fluid was obtained. Exploration revealed a perforation on the greater curvature of the fundus of the stomach approximately 1.5 cm. in length with retraction of the serosal muscular layer. Several cubic centimeters of bile-stained material was aspirated from the perforation. The opening was closed with 00 Duloc absorbable surgical (gut) and reinforced with 00000 black nonabsorbable surgical (silk) sutures. The abdominal wall was then closed in layers.

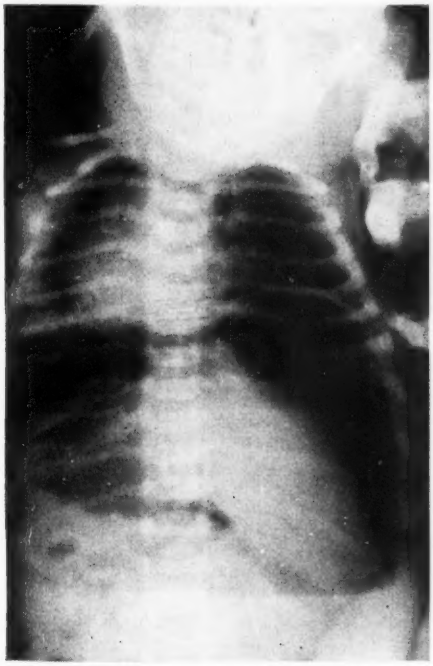

Fig. 2.—Flat plate and upright x-ray film of abdomen revealing pneumoperitoneum.

The postoperative course was uneventful for three days, when the patient again regurgitated his feedings and the abdomen became distended. Mechanical intestinal obstruction was suspected, and a gastric tube was passed. X-rays of the abdomen showed paralytic ileus. The next day generalized edema was observed, probably to overhydration and hypoproteinemia. Total protein was 5.9 gm./100 cc., nonprotein nitrogen 23 mg./100 cc. After 48 hours, feeding was resumed and the edema was greatly decreased. At the time of discharge, four weeks after operation, the patient was eating well and gaining in weight. The child has remained well and was developing normally when seen three years later.

Summary

Two cases, one of perforated duodenal ulcer and one of ruptured stomach in newborn infants, are reported. Both patients survived surgical repair.

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Editorial

DEATHS FOLLOWING STERNAL PUNCTURE

ARINKIN in 1927 described a method of diagnoses of hematopoietic diseases by needle aspiration.[1] His method of examination of sternal marrow particles and aspirating material has since become a valuable procedure in the diagnoses and treatment of other types of diseases. For many of these diseases it is the only positive means of diagnoses.[2]

The comparatively simple procedure of sternal puncture is normally without danger to the patient. However, when some undetermined pathological condition of the sternum is present, such as a softening of the inner or both plates of the sternum, due to neoplastic or other disease, a plain needle used for sternal aspiration may be forced through the inner plate into the heart and large blood vessels. Fatalities have resulted from the unknown pathological condition of the inner plate of the sternum when a simple needle was used, but only a few of these fatalities have been reported.*

Much credit should be given to those reporting these accidental fatalities, for they serve to warn others of the use of unsafe needles for sternal punctures.

Quoting from the editorial of *The Journal of the American Medical Association* on "Deaths Following Sternal Puncture,"[15] which refers to another *Journal of the American Medical Association* editorial on "Intraosseous Infusions"[16]: " 'the hazards of perforation through the entire sternum or ilium due to too sudden or a forceful thrust of a pointed needle has also been eliminated through the use of the trephine needle, which permits controlled pressure'. Since the technique of insertion for sternal puncture and infusion is identical, deaths following either of these two procedures can be minimized by the use of a trephine-type instrument that permits controlled pressure. Cases are on record in which as many as 70 sternal punctures have been made during chemotherapeutic studies on leukemic patients and in all cases trephine-type instruments were used. The safety features embodied in this type of instrument obviate preventable deaths due to sternal puncture."[17] "If additional fatalities occur because of the use of unsafe instruments this valued diagnostic procedure may fall into disrepute."[17]

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Case Reports

INTRAHEPATIC CALCULUS AND ABSCESS

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LIVER abscesses are not uncommonly the sequelae of cholangitis due to extrahepatic calculus obstruction. However, the conjunction of abscess and intrahepatic stone is rare. In a recent review,[1] only 29 cases had been reported in the world's literature to 1952. Of these, 12 received definitive therapy in the form of surgical drainage, with 5 surviving operation. The sixth such case is the subject of this communication.

A 38-year-old white married woman was admitted to the Manhattan General Hospital on Oct. 10, 1955. She complained of epigastric pain of four days' duration. The pain was continuous in character, with minor exacerbations and remissions. It did not radiate and was unaccompanied by nausea, vomiting, or bowel change. A daily temperature rise to 102 F without chills was noted. There were no symptoms referable to other portions of the body. She had had a salpingectomy for tubal pregnancy in 1940. There was no history of recent upper respiratory infection, focal inflammation, amebic disease, or gastrointestinal disease.

On admission, the temperature was 100.4 F; the pulse rate, 90; respirations, 22, and the blood pressure, 125/80. There was no clinical evidence of jaundice. The only abnormal finding was moderate tenderness and rigidity localized over a mass situated just distal to the xiphoid. The mass was poorly delineated, measured approximately 15 cm. in diameter, and moved with respiration. The liver edge was not palpable. Blood studies revealed 14.5 gm. per 100 cc. of hemoglobin, a red cell count of 4,529,000, and a white cell count of 11,850. The differential count showed 73% polymorphonuclear leucocytes, with 6% staff forms, 3% eosinophiles, 1% monocytes, and 23% lymphocytes. The only abnormal urinary finding was a slight trace of albumin.

The patient was explored, during endotracheal anesthesia, through a right subcostal incision. The previously palpated mass was found to be densely infiltrated omentum, adherent to the anterior aspect of the left lobe of the liver and the falciform ligament. As the mass was separated from the liver, an abscess cavity containing about 100 cc. of thick white pus was entered. This extrahepatic abscess communicated through a short narrow sinus tract with another abscess, located in the center of the left lobe of the liver. The parenchymal abscess was about 5 cm. in diameter. It contained the same type of pus and a free-lying calculus. The stone was white, smooth, and spherical. Its diameter measured 1.3 cm., and its cut surface presented fine lamellations. The wall of the abscess showed a gross inflammatory reaction for a depth of 1 cm.

The supraduodenal portion of the common duct was exposed and found to be completely normal, with an external flat diameter of 8 mm. The gall bladder appeared normal, and its interior was inspected through an incision in the fundus. Normal bile was evacuated, and the mucosal aspect of the gall bladder appeared completely normal. A de Pezzer catheter was sutured into the cholecystostomy for subsequent cholangiography. Palpation of the colon and pelvis revealed no abnormalities. The stomach from pylorus to esophagus was visualized, without detection of any disease. The involved segment of liver including the entire abscess and its wall was resected, with use of absorbable surgical (gut) mattress for hemostasis. The abdominal wall was closed with buried figure-eight Stainless Steel wire sutures and nonabsorbable surgical (silk) sutures to the skin. A drain to Morison's pouch was brought through a lateral stab wound.

The postoperative course was completely benign. On the seventh postoperative day iodopyracet (Diodrast) was instilled into the cholecystostomy tube and x-ray revealed a completely normal gall bladder and extrahepatic duct system, with rapid flow into the duodenum. The drain was removed on the 8th day, and the cholecystostomy tube, on the 10th postoperative day. The patient was discharged 18 days after admission with a firm wound and no further external drainage.

Culture of the pus on both aerobic and anaerobic media was sterile for 96 hours. Blood chemistry studies on the first postoperative day showed a serum cholesterol of 125 mg. per 100 cc.; cholesterol esters, 58.2 mg. per 100 cc.; bilirubin, 1.1 mg. per 100 cc., with 0.85 mg. of the direct-reacting type; a negative cephalin-flocculation test within 48 hours, and a normal red cell fragility. Inspection of repeated stools failed to detect any amebae,

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parasites, or ova. The stone consisted of virtually pure calcium phosphate, without a trace of cholesterol or pigment on chemical assay. On microscopic examination the wall of the abscess disclosed chronic nonspecific inflammation without detectible bacteria or amebae.

Comment

Intrahepatic calculi have been found in 5% to 15% of carefully necropsied cases of cholelithiasis (Thudicum, 1863, 5%; Schroder, 1890, 9%; Wolynzew, 1904, 16%; Beer, 1904, 8.3%; Miyake, 1913, 7.2%; Best, 1944, 6.6%). In one out of five reported cases of intrahepatic lithiasis the stones were confined to the liver, with none in the extrahepatic biliary tract.[2]

Galambos [3] has rightly divided the cases of intrahepatic stone into three subgroups on the basis of the presumed site of stone formation: A. The stones arose in the extrahepatic biliary tract and migrated to the liver. These form the vast majority of reported cases of intrahepatic calculi. B. There are intrahepatic calculi which arose in the liver as well as other calculi, usually of a different type, formed and found in the extrahepatic biliary tract. This group is relatively small. C. The stones are formed within the liver while the gall bladder and extrahepatic ducts are free of pathology. Very few cases belong to this group of "true, pure, intrahepatic lithiasis."

In the case reported here, the findings at operation supported by subsequent cholangiography strongly suggest that the calculus was formed within the liver substance. From its size, shape, chemical nature, and location, it probably represents a calcific deposit which is the result rather than the cause of the surrounding parenchymal inflammation. The pathogenesis of the abscess in this case could not be determined. A similar cryptogenic origin of pyogenic liver abscesses was found in 59.9% of 47 cases reported by Ochsner, DeBakey, and Murray [4] and 45.8% of 24 solitary pyogenic abscesses studied by Rothenberg and Linder.[5]

Although surgical drainage as practiced in all the previously reported survivors might have sufficed; in this case the involved segment of liver was excised. This procedure was elected because of the technical ease with which it could be performed and the remote possibility that the solitary abscess might have been due to degeneration of a local neoplasm.

Summary

The sixth case of combined intrahepatic abscess and calculus successfully treated by surgery is reported. It is predicated that in this case the calculus represented the sequela of a primary cryptogenic liver abscess.

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